BY THE COMPTROLLER GENERAL

Report To The Honorable
Paula Hawkins
United States Senate
OF THE UNITED STATES

Improvements Needed In Clinical Testing Of Anticancer Drugs

Despite improvements in the way the Food and Drug Administration (FDA) and the National Cancer Institute (NCI) have carried out their responsibilities of protecting patients during clinical testing of anticancer drugs, further improvements should be made.

Actions needed by FDA include (1) more promptly notifying sponsors of clinical drug tests of concerns raised during its review of study proposals, (2) establishing a followup system to assure that its concerns are addressed by sponsors, (3) requiring sponsors to submit all study plans (protocols) before clinical testing begins, (4) clarifying its requirements for the reporting of adverse drug reactions, and (5) issuing final regulations specifying the monitoring responsibilities of sponsors.

Actions needed by NCI include (1) advising FDA in a timely manner of actions taken or to be taken on concerns raised by FDA, (2) requiring that site monitoring visits be made frequently enough to assure that the studies are properly carried out, and (3) studying the need for and usefulness of its drug study data system and, if needed, requiring that data be submitted in a more timely and complete manner.

GAO/HRD-83-52
SEPTEMBER 26, 1983

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COMPTROLLER GENERAL OF THE UNITED STATES
WASHINGTON D.C. 20548

B-212322

The Honorable Paula Hawkins
United States Senate

Dear Senator Hawkins:

In response to your December 7, 1981, request, we have reviewed the clinical testing of anticancer drugs and the regulation of that testing by the Food and Drug Administration (FDA).

Our review was directed to determining (1) how well FDA, during its review of investigational new anticancer drug applications and amendments thereto, discharges its responsibility to protect human test subjects; (2) the manner in which drug sponsors and institutional review boards carry out their responsibilities; and (3) whether there is therapeutic intent during phase I testing of anticancer drugs.

As arranged with your office, unless you publicly announce its contents earlier, we plan no further distribution of this report until 30 days from its issue date. At that time we will send copies to interested parties and make copies available to others upon request.

Sincerely yours,

Charles A. Bowsher

Comptroller General
of the United States

COMPTROLLER GENERAL'S REPORT TO THE HONORABLE PAULA HAWKINS UNITED STATES SENATE

IMPROVEMENTS NEEDED IN CLINICAL TESTING OF ANTICANCER DRUGS

D I G E S T

This year over 400,000 Americans will die of cancer, while over 800,000 will develop the disease. In the 1930s only one in five cancer patients had any hope of long-term survival. By 1982, the 5-year survival rate had improved to better than one in three.

One of the major factors contributing to an improved survival rate of cancer patients has been the development of anticancer drugs. The testing of these drugs has been sponsored largely by the National Cancer Institute (NCI) which currently spends over $1 billion a year on the development of anticancer drugs and to a lesser extent by private firms.

Although the survival rate for cancer patients has been improving, a majority of cancer patients will die within 5 years. This is particularly true of patients entering experimental drug tests because conventional treatment has failed or not been available. Therefore, patients are probably willing to accept a higher degree of risk when using such drugs than would other types of patients using more proven drugs. But even in such situations, there may be unnecessary risks that should be avoided.

There are four key participants in the testing of anticancer drugs--the Food and Drug Administration (FDA) which is responsible for regulation of the process; drug sponsors, such as NCI or a pharmaceutical company, who provide funding for testing and developing the drugs; clinical investigators, usually physicians, who actually conduct the tests by administering the drugs and reporting results; and the patients who receive the drugs. Experimental anticancer drug studies are conducted under protocols (study plans) which are developed by clinical investigators and submitted by the sponsors to FDA. The sponsors must wait at least 30 days before beginning clinical testing to give FDA time to determine

GAO/HRD-83-52
SEPTEMBER 26, 1983

Tear Sheet

whether it has any safety concerns with the proposed study. When additional protocols or amendments to existing protocols are submitted, the investigator is not required to wait 30 days before beginning testing.

This review was made at the request of Senator Paula Hawkins to determine the adequacy of the management and operation of NCI's drug development program and FDA's regulation of these activities.

PROTECTION OF PATIENTS IMPROVING

Since a 1976 GAO review and 1981 congressional hearings, FDA and NCI have made or are making improvements to better ensure that patients involved in clinical testing of anticancer drugs are protected. These improvements include:

--More monitoring of investigators who perform the clinical studies for the sponsors.

--Improved reporting of adverse drug reactions.

--Increased controls over investigational drug supplies.

During this study, GAO selected 10 of the estimated 100 anticancer drugs currently undergoing testing and traced their progress through the testing process. GAO found that the process of assuring that patients are fully informed about the risks and benefits of participation in the drug study was generally carried out according to FDA regulations, and clinical investigators generally were complying with protocol requirements. (See p. 21.)

GAO also found that additional actions are needed to more fully assure that patients are adequately protected during the clinical testing of anticancer drugs.

DEFICIENCY LETTERS

FDA procedures provide for notifying drug sponsors of safety concerns with proposed studies within 30 days after receipt of the study plan. Formal notification of these and other concerns are contained in deficiency letters. GAO found that delays by FDA reviewers in completing written reports on deficiencies identified in

applications for the testing of new drugs resulted in FDA sending deficiency letters to sponsors 2 to 5 months after an application was received. According to FDA officials, inadequate numbers of clerical staff contributed to this problem.

Although sponsors are notified of the most serious deficiencies by telephone within 30 days, they are not advised of other deficiencies which could affect patient safety until after clinical testing has started. In one case, an FDA pharmacologist's review was not completed until 71 days after the application was received. The pharmacologist recommended that patients be closely observed for a number of possible toxicities. The deficiency letter was not sent to the sponsor until 2 months after clinical testing began. No evidence could be found that the sponsor was advised of the pharmacologist's concerns before receiving the deficiency letter. This deficiency was not discussed when the sponsor was advised informally that clinical testing could begin. (See p. 9.)

FDA FOLLOWUP OF IDENTIFIED DEFICIENCIES

Although FDA has authority to halt or delay clinical studies if sponsors do not correct problems which could affect patient safety, it does not have a system to assure that sponsors have taken action to correct problems brought to their attention by FDA. As a result, it is not always known whether FDA's concerns have been acted upon. GAO found, based on its review of 10 drug studies, two instances where FDA recommendations were not implemented by sponsors and the sponsors did not inform FDA that action was not being taken. In one case FDA recommended that a sponsor exclude from a new drug study patients who had previously taken another drug because of the potential for heart damage. After FDA started receiving reports of patients experiencing heart damage, it discovered that its recommendation to exclude such patients from clinical testing had not been implemented. (See p. 12.)

FDA REVIEW OF AMENDMENTS TO CLINICAL STUDIES

FDA regulations are not clear on whether amendments to an already active drug study must be

submitted to it for review. As a result, sponsors do not always submit amendments to FDA for review and, when they are submitted, FDA frequently does not review them or does not review them in a timely manner. Since amendments, such as new protocols, can significantly change a study, FDA cannot determine whether it has any safety concerns and whether patients are adequately protected unless it reviews them. For example, GAO found 12 protocols involving five drugs that had not been submitted to FDA for review. In three of these cases, the investigator had not notified the sponsor that clinical testing was beginning. GAO also reviewed 186 amendments submitted to FDA and found that 44 took 30 days or more to review and 48 were not reviewed at all. (See p. 14.)

REPORTING OF ADVERSE DRUG REACTIONS

FDA regulations are not specific regarding the (1) definition of adverse drug reactions and (2) time frames in which these reactions should be reported to FDA. In addition, it is difficult for clinical investigators and sponsors to determine in many instances whether a change in a patient's condition is caused by the investigational drug or by some other factor, such as the patient's cancer. Reporting all patient reactions as adverse drug reactions could lead to an unmanageable number of such reports being forwarded to FDA. On the other hand, nonreporting of adverse reactions could jeopardize patient safety.

Problems in defining an adverse drug reaction appeared to contribute to sponsor and investigator delays in reporting adverse reactions on several drugs. One sponsor (NCI) has attempted to solve the problem by issuing guidelines to its clinical investigators regarding adverse drug reaction definitions and reporting time frames. (See p. 25.)

MONITORING OF CLINICAL INVESTIGATORS

NCI's visits to monitor investigators' performance and control of drug supplies are an important means of determining whether investigators are properly carrying out their responsibilities and whether patients are treated safely. These visits serve as a means of determining whether clinical investigators are (1) following drug

study protocols, (2) accurately reporting drug study results, and (3) following proper informed consent procedures. GAO found that NCI does not require monitoring visits to many of its investigators but plans this year to expand the number of investigators visited.

Also, the frequency of monitoring visits to some of NCI's investigators (an average of once every 3 years) may not be enough to determine that investigators are performing properly because the studies may be completed before the end of the 3-year period. For example, an NCI study showed that private firms visited their investigators an average of seven times a year. NCI believes that its random process of selecting investigators to be visited will prevent them from becoming complacent in performing their duties. (See p. 38.)

RECOMMENDATIONS TO THE SECRETARY OF HEALTH AND HUMAN SERVICES (HHS)

GAO is recommending that sponsors of clinical studies be required to approve and submit to FDA all clinical protocols before clinical studies begin and that FDA establish a formal followup system to assure that sponsors have acted on its concerns. This report contains other recommendations to the Secretary for actions by FDA and NCI to improve protection of patients during clinical testing of anticancer drugs. (See pp. 17, 33, and 46.)

AGENCY COMMENTS AND GAO EVALUATION

HHS agreed that certain administrative improvements were needed and outlined actions it has taken or will be taking to ensure that risks to patients are minimized. Planned actions include establishing a specific requirement that sponsors submit new protocols to FDA before beginning clinical testing under the new protocols.

HHS made an overall comment that the report could appear to incorrectly imply that cancer patients are being exposed to unnecessary risks based on procedural deficiencies. HHS said that procedural deficiencies that could or might imply risk do not establish risk. GAO agrees that such a distinction

is useful and valid. However, certain of the deficiencies identified by GAO, such as FDA's not reviewing new protocols before testing begins and not assuring that its concerns have been addressed by test sponsors, could have the potential of exposing patients to unnecessary risks.

HHS disagreed with GAO's recommendation that FDA's drug reviewers discuss all deficiencies with sponsors of investigational new drugs before clinical testing begins, or as soon as possible after a deficiency is noted if testing has already begun, believing that it is necessary to discuss immediately only the deficiencies which significantly affect patient safety. However, GAO believes that the concerns not discussed--such as drug purity--are also significant and should be discussed immediately particularly in view of the time required to issue deficiency letters. GAO has modified its recommendation to provide that if discussion of all deficiencies is not always feasible that a definition of significant deficiencies be developed to guide FDA reviewers in deciding which safety-related problems to discuss with sponsors.

HHS also disagreed with the recommendation that NCI, if possible within allocated resources, increase the frequency of site visits to monitor investigators' performance believing that the present level of monitoring is adequate because investigators do not know when they will be site visited. GAO continues to believe that the frequency of visits should be increased because drug studies could be completed before visits are made and the need for frequent visits is evidenced by the practice of private sponsors.

Contents

ABBREVIATIONS

ADR	adverse drug reaction
FDA	Food and Drug Administration
GAO	General Accounting Office
HHS	Department of Health and Human Services
IND	investigational new drug
IRB	Institutional Review Board
NCI	National Cancer Institute

CHAPTER 1

INTRODUCTION

This year over 400,000 Americans will die of cancer, while over 800,000 will develop the disease. Although these figures sound ominous, they should not obscure the fact that advancements in cancer treatment methods have continually increased the patient survival rate.[1] Current treatment methods generally consist of surgery, radiation, chemotherapy (the use of drugs), or a combination of these methods. Recent studies show that such treatment has increased the patient survival rate from one in five patients in the 1930s to better than one in three today.

Chemotherapy in particular has contributed greatly to the survival rate increase. Most anticancer drugs are "cytotoxic"; in other words, they have a toxic effect on cells of certain organs. Unfortunately, the same toxicity that kills cancer cells can also kill normal cells. Therefore, researchers are attempting to find drugs whose toxic effects will be directed more toward the rapidly producing cancer cells than the body's noncancerous cells.

Cytotoxic drugs can be effective in treating some types of cancer and ineffective in treating others. More than 100 forms of the disease exist, and various treatment methods must be found to deal with them.

Although the survival rate for cancer patients has been improving, patient deaths are still more likely to be the norm than the exception. This is particularly true of patients entering experimental drug tests because conventional treatment has failed or not been available.

DRUG DEVELOPMENT AND TESTING

There are four key participants in the testing of anticancer drugs--the Food and Drug Administration (FDA) which is responsible for regulation of the process; drug sponsors, such as the National Cancer Institute (NCI)[2] or a pharmaceutical company, who provide funding for the testing and develop the drugs; clinical investigators, usually physicians, who actually conduct the tests by administering the drugs and reporting results; and the patients who receive the drugs.

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[1]Patient survival is defined as being alive 5 years after treatment begins.

[2]NCI is 1 of 11 institutes in the Department of Health and Human Services' (HHS') National Institutes of Health.

NCI is the primary force behind the development of new anticancer drugs spending over $1 billion a year on this activity. Because of the poor profit potential of the drugs, private pharmaceutical companies are involved to a much lesser extent. NCI screens thousands of compounds every year with hopes that a promising new chemical agent will be discovered. When the laboratory screening process reveals a drug that shows potential for treating selected tumors, the drug undergoes toxicology tests in animals.

The purpose of animal toxicology tests is to identify for future human studies what the initial starting dose should be, what toxicities can be expected from the drug, whether cumulative toxicities are possible with repeated doses, and whether the toxicities are reversible. Drugs which appear promising during animal testing progress to clinical studies where the first human testing takes place.

The clinical testing program has three phases which differ both in their purpose and in the numbers of patients involved. The purpose of phase I drug studies is to determine the safe dose range, the preferred method of drug administration, and the human body's reaction to the drug. The measurement of drug effectiveness is not a major purpose of this phase. Phase I studies of anticancer drugs involve a small number of terminally ill patients[3] who have not benefited from standard treatment or who have a type of cancer for which effective standard treatment is not available. When phase I studies are successfully completed, phase II can begin. In this phase, drugs are tested for effectiveness against certain tumor types; various dose schedules may also be tried. More investigators test the drug in this phase, and more patients are involved. If, as a result of phase II studies, the drug is shown to produce benefits which exceed risks, testing moves on to phase III. The purpose of phase III is to compare the new drug with alternative drugs and treatment methods and to determine the types of cancer for which the new drug works better than existing drugs. If a drug appears to be safe and effective as a result of the phase I to III studies, the sponsor may submit a new drug application to FDA for approval to market the drug.

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[3]In this respect, testing of anticancer drugs is different than phase I testing of most other drugs. With other drugs, healthy volunteers are used.

THE REGULATORY PROCESS[4]

Before the aforementioned clinical testing may be initiated, the drug's sponsor must submit to FDA a "Notice of Claimed Investigational Exemption for a New Drug," also known as an IND (investigational new drug). The initial IND submission to FDA must include a package of information containing

--information on the chemical composition of the drug;

--data on the manufacturing process;

--data from preclinical investigations, including animal tests;

--the study plan, or "protocol," for the proposed study;

--information on the investigators (physicians) who will conduct the study; and

--copies of informational material supplied to each investigator.

The protocol is a key document because of the important information it contains. The protocol includes an estimate of the number of patients to be treated with the drug; clinical uses to be investigated; characteristics of patients by age, sex, and condition; the kind of clinical observations and laboratory tests to be undertaken before, during, and after administration of the drug; the estimated duration of the investigation; and a description or copies of report forms to be used to maintain an adequate record of the observations and test results obtained.

According to FDA regulations, the sponsor must also notify FDA and all investigators of adverse effects occurring during animal or human testing, must get the investigator's agreement to obtain the informed consent of patients before giving them the drug, and must submit annual progress reports to FDA.

The sponsor may not begin administering the drug to humans for 30 days after submitting the IND to give FDA time to determine whether it is safe to proceed with the sponsor's proposed testing. The IND application is reviewed by a team consisting of a medical officer, a pharmacologist, and a chemist. If the team raises concerns about the safety of the proposed clinical

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[4]Unless otherwise indicated, the requirements discussed in this section are contained in 21 C.F.R. 312.1(a).

tests, FDA can hold up the testing until its concerns are resolved. If FDA does not notify the sponsor within the 30-day period, clinical testing may begin. Subsequent submissions (amendments) are not subject to the 30-day requirement.

The sponsor's role, beyond submitting the initial IND package to FDA, is to keep track of ongoing clinical studies and provide FDA with required information about the studies. Additional protocols for clinical studies, changes to the studies, annual reports, and reports of patient adverse drug reactions (ADRs) are examples of information a sponsor provides to FDA during a drug study. Much of the information originates with the clinical investigator, who is responsible for administering the drug to the patients. The investigator designs the study protocol, establishes and applies eligibility criteria, conducts the clinical studies, and sends reports on the studies to the sponsor and the institutional review board (IRB).[5]

At institutions where drug testing takes place, IRBs conduct initial and ongoing reviews, making sure that risks to patients are reasonable in relation to anticipated benefits (see 21 C.F.R. 56.111(a)(2)(1982)). IRBs consider such matters as the process for obtaining informed consent from patients who will be subjects of a drug study, changes in research activity, unanticipated problems that could involve risks to patients, and instances of investigator noncompliance with IRB requirements.

Finally, in addition to reviewing the initial IND application, FDA also reviews subsequent submissions of information during the course of the drug studies. Subsequent submissions may include additional protocols or changes to the study, annual reports, or reports of ADRs. Patient safety is a primary concern of FDA in its IND process. FDA is empowered to stop drug testing at any time if it determines that patient safety is not being adequately considered.

RECENT CONGRESSIONAL HEARINGS CONCERNING CLINICAL TESTING OF ANTICANCER DRUGS

Congressional hearings were held in 1981 and 1983 focusing on various aspects of the development of anticancer drugs. These included:

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[5]An IRB is any board, committee, or other group formally designated by an institution to review, approve the initiation of, and conduct periodic reviews of biomedical research involving humans (21 C.F.R. 56.102(g)(1982)).

--Hearings by the Subcommittee on Investigations and Oversight, House Committee on Science and Technology, in April 1981 concerning ethical and institutional problems in biomedical research.

--Hearings by the Subcommittee on Investigations and General Oversight, Senate Committee on Labor and Human Resources, in May 1981 on oversight of the national cancer program and the last 10 years of progress toward a cure for cancer.

--Hearings by the Senate Committee on Labor and Human Resources in June 1981 concerning NCI contracting procedures.

--Joint hearings by the Subcommittee on Health and the Environment, House Committee on Energy and Commerce, and the Subcommittee on Investigations and Oversight, House Committee on Science and Technology, in October 1981 regarding NCI's therapy program.

--Hearings by the Subcommittee on Investigations and General Oversight, Senate Committee on Labor and Human Resources, in November 1981 concerning the use of experimental drugs on cancer patients.

--Hearings by the Senate Committee on Labor and Human Resources in June 1983 on the current status of the anticancer drug development program.

PRIOR GAO REPORT

In our report "Federal Control of New Drug Testing Is Not Adequately Protecting Human Test Subjects and the Public" (HRD-76-96, July 15, 1976), we reported that FDA was neither adequately monitoring new drug tests nor adequately enforcing compliance with testing requirements. Consequently, we concluded that FDA lacked assurance that (1) the thousands of humans involved in such tests annually were protected from unnecessary hazards or (2) the test data used in deciding whether to approve new drugs for marketing were accurate and reliable.

We made recommendations to improve monitoring and enforcement processes in clinical investigations, the informed consent process for patients participating in clinical studies, FDA's knowledge of IRBs, and coordination of inspection and regulatory activities of FDA's Bureau of Drugs and Bureau of Biologics. Additionally, we recommended that the Congress clarify the applicability of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 301 et seq.) to the regulation of clinical testing of new drugs by Federal agencies and departments.

FDA has, or is in the process of acting on, all of the recommendations. FDA's proposed sponsor-monitoring regulations will further address the monitoring aspects. Regarding our recommendation that informed consent forms be reviewed by FDA before clinical investigations begin, FDA contended that the intent of the recommendation was met by the requirement that IRBs review informed consent forms. The Congress did not take any action on our recommendation to it.

OBJECTIVES, SCOPE, AND METHODOLOGY

We performed this review at the request of the Chairman, Subcommittee on Investigations and General Oversight, Senate Committee on Labor and Human Resources.[6] The Chairman asked that we study the adequacy of existing policy, practices, and procedures within HHS and its subagencies regarding protection of humans who participate in federally sponsored testing of investigational new drugs. The Chairman indicated that she was primarily interested in anticancer drugs. We therefore agreed, with the Subcommittee's approval, to concentrate on them.

The Chairman expressed particular concern about the management and operation of NCI's drug development program and FDA's regulation of these activities. Additionally, the Chairman asked that the study compare FDA's regulatory procedures for federally and privately sponsored clinical studies. In line with the Chairman's requests, our study had the following objectives:

--To assess how well FDA, during its reviews of IND applications and amendments thereto, discharges its responsibility to protect patients participating in the studies.

--To assess the manner in which drug sponsors (NCI and private firms) and IRBs carry out their responsibilities.

--To determine whether there is therapeutic intent (i.e., an intent to help patients) during phase I testing of anticancer drugs.

The Chairman also asked that we compare the way FDA regulates and monitors NCI's clinical studies with the way it regulates and monitors privately sponsored studies of anticancer

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[6]This Subcommittee was abolished in the present session of the Congress. As agreed with the Chairman's office, this report is being issued to Senator Paula Hawkins, who was chairman of the Subcommittee.

drugs. We did not note any inconsistencies in the way FDA regulates and monitors NCI with the way it regulates and monitors private sponsors.

To accomplish these objectives, we selected a sample of 10 investigational drugs currently undergoing testing and traced their progress through the regulatory process from the time FDA first received the IND application until our cutoff date of October 1, 1982. Our sample was limited by the large volume of documents at FDA, sponsors, and institutions relating to each of these drugs. All 10 drugs were cytotoxic anticancer drugs with active INDs. Six NCI-sponsored drugs and four privately sponsored drugs were chosen so that a comparison could be made of the IND process for publicly and privately sponsored drugs. Each of the privately sponsored drugs had a different sponsor. We tried to obtain a mix of "old" and "new" drugs. Five drugs had been submitted to FDA before 1981 and five in 1981. We did not select any drugs submitted after 1981 because clinical testing would not have started when we started our review. As of April 1, 1983, none of our sample drugs had been approved for general marketing; all but one were still in phase I or phase II testing.

The universe of cytotoxic anticancer drugs (see p. 1) from which we selected our sample could not be readily determined because FDA records do not separate (1) cytotoxic drug INDs from other types of anticancer drug INDs; (2) treatment (compassionate) INDs, which do not involve research and may include only one patient, from full scale research INDs; or (3) physician sponsored and institution sponsored INDs from NCI and private drug company INDs. Obtaining this information would have required reviewing the voluminous files on all the INDs. Since we did not plan to project the results of our sample to any universe of cytotoxic drugs, we did not attempt to separate the specific number of cytotoxic INDs as a whole or by category. One FDA official estimated that there were about 100 active anticancer drug INDs sponsored by NCI and by private drug companies, excluding compassionate INDs as of May 1983.

To assess patient protection from unnecessary risks in the IND program, we reviewed policies, procedures, and practices at FDA, sponsor, and institutional levels. We examined FDA's initial and ongoing reviews of IND applications for our sample drugs to determine the adequacy and timeliness of its reviews. We visited NCI and private sponsors to obtain information on monitoring and testing practices for new drugs. We also visited eight institutions where clinical tests on the 10 sample drugs had taken place or were ongoing. At these institutions, we met with clinical investigators and representatives of IRBs and reviewed 171 patient files.

In addition to verifying that IRBs were performing their federally mandated functions regarding patient safety, we examined patient files, where applicable, and determined whether patients had signed informed consent forms, were eligible for the drug study according to protocol requirements established by the investigator, and whether investigators had conducted their tests according to specifications outlined in the protocol regarding patient testing. Since we did not have authority to review private sponsors' files, we were limited to information that the sponsors voluntarily gave us or allowed us to examine. In some cases, therefore, we were not able to review all information that may have been applicable to our study.

Our fieldwork was performed from January 1982 to March 1983 and except as noted above was done in accordance with generally accepted governmental auditing standards.

CHAPTER 2

ADMINISTRATIVE AND WORKLOAD PROBLEMS HAMPER FDA'S REVIEW OF INVESTIGATIONAL NEW DRUG APPLICATIONS

Without adequate and timely review of IND applications and amendments, FDA cannot be assured that patients are safeguarded against unnecessary risks. Although FDA appears to complete its safety review of initial IND applications in a timely manner, documentation is not always available to prove it. After the reviews are completed, FDA is slow in sending deficiency letters to IND sponsors and does not follow up to assure that sponsors are addressing the concerns cited in these letters. Sponsors do not always submit IND amendments to FDA for review, and when submitted, FDA frequently does not review them promptly. These problems, according to FDA officials, have been caused primarily by limited staff resources.

FDA'S TIMELY REVIEW OF INITIAL INDS NOT ALWAYS VERIFIABLE

Although initial safety reviews of IND applications appear to be timely, FDA could not always provide written evidence that these reviews were completed. FDA regulations require sponsors to wait 30 days after submitting their application before beginning clinical studies. This gives FDA time to review the application to make certain that it contains the necessary information and that patients will not be exposed to unwarranted risks. While neither FDA regulations nor guidelines require that safety reviews conducted during this 30-day period be documented, we believe that written evidence of such reviews is good management practice.

We verified written evidence of safety reviews for 5 of the 10 drugs included in our review. FDA reviewers documented these reviews by noting completion of the safety review on a transmittal memorandum and/or completing a formal written report within the 30-day period. For the other five drugs, FDA reviewers could only tell us orally that they had performed safety reviews within the required time frame.

The IND files for these five drugs did not contain documentation that the pharmacologist's safety reviews were completed. The pharmacologist told us that safety reviews for these drugs had been performed and documented but could not give us written evidence on when they were completed. The pharmacologist told us that the safety review transmittal document is frequently misplaced.

Some FDA officials stated that delays in the reviewers receiving the IND application sometimes prevent FDA from performing safety reviews in a timely manner. Although we did not note examples of this, one reviewer told us that three or four times a year delays in receiving IND applications will cause reviewers to miss the 30-day time frame. Other FDA officials confirmed that delays in the mailing and routing systems for incoming documents frequently hamper the review process.

Six of the 10 IND applications we reviewed took from 10 to 20 days to reach the FDA review team. For example, FDA received an IND application for one drug on December 31, 1981, but the responsible pharmacologist did not receive this application for review until January 12, 1982--12 days later. The chemist did not receive the application until January 20--20 days later. The reviews were completed on January 25 and 26, 1982, respectively.

Our basic concern in this matter is that reviewers may not have adequate time to thoroughly review IND submissions before clinical testing is allowed to begin. FDA records should show (1) that the reviewers have completed their review, (2) what concerns were raised, and (3) that those concerns were transmitted to the sponsor.

In commenting on a draft of this report, HHS expressed concern with the statement that delays in distributing INDs to FDA reviewers may cause them to miss the 30-day safety review time frame. HHS stated that there still was ample time to perform the 30-day safety review before initiating the clinical study. HHS stated that statistical data from FDA's management information system showed that only 4 of 3,336 INDs received for all drug categories from October 1980 through March 1983 were not reviewed within the 30-day limit. According to FDA officials, these data were compiled using safety review transmittal documents. We question the accuracy of these data since our review of selected drug files showed that these documents could not always be located. Further, an FDA official responsible for compiling these data stated that the accuracy of these statistics are questionable.

FDA SLOW IN SENDING DEFICIENCY LETTERS TO IND SPONSORS

In some instances clinical testing may begin before sponsors have an opportunity to address FDA concerns. When FDA has major concerns about patient safety, sponsors are to be notified by telephone. These concerns are then addressed in deficiency

letters. Regulations do not specify when FDA must send deficiency letters to IND sponsors.[1] For the 10 drugs reviewed we found that delays in completing written reviews (24 to 179 days) coupled with staff shortages resulted in FDA sending deficiency letters to sponsors an average of 86 days after the IND was received. FDA requires that written reviews be completed in not more than 60 days after FDA receives the IND.

FDA telephones IND sponsors before the end of the 30-day review period to inform them of significant deficiencies that will jeopardize patient safety. If not corrected, these deficiencies are of the type that would warrant holding up the clinical study. However, our review disclosed that FDA does not inform sponsors over the telephone of other less serious deficiencies--including questions about the purity of a drug--that could compromise patient safety. FDA subsequently addresses these problems in the deficiency letters to sponsors.

FDA deficiency letters were sent late to IND sponsors partly because FDA reviewers had not promptly documented safety reviews. These letters are prepared by consolidating recommendations from each of the reviewer's written safety reviews. For 2 of 10 drugs we reviewed, written reviews which are the basis for the deficiency letters, took more than 60 days to be completed. FDA received an IND application for one of these drugs on April 12, 1979. The pharmacologist's report, which included a request that the sponsor submit the results of studies involving appropriate animal models comparing cardiotoxicity problems with adriamycin (an approved anticancer drug), was completed on June 15, 1979. The deficiency letter which included this concern was sent August 6, 1979, 3 months after clinical testing began.

In the other case the pharmacologist's written review was not completed until March 11, 1982, 71 days after FDA received the IND. The pharmacologist requested that patients be closely observed for phlebitis, gastrointestinal toxicity, myelosuppression, and central nervous system toxicity. The deficiency letter which included this concern was not sent to the sponsor until May 4, 1982, 2 months after clinical testing began. We could find no evidence that the sponsor was advised of the pharmacologist's concerns before receiving the letter.

According to FDA, shortages of clerical staff also contribute to delays in sending deficiency letters to sponsors. We noted that after reviewers have completed their reviews, delays are encountered in getting their reports typed. FDA officials

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[1]See 21 C.F.R. 312.1(a)(2)14(1982).

told us that the heavy workload has placed a tremendous typing burden on the clerical staff. FDA has one secretary and one clerk typist to perform administrative tasks on anticancer drugs. FDA officials told us that the administrative support given to anticancer drug review is approximately that given to other drug groups.

One FDA official told us that sending deficiency letters late is not a problem because he felt the deficiencies not discussed on the telephone were not safety related or did not need to be addressed during phase I testing. However, in addition to some medical officer and pharmacologist concerns not being discussed over the telephone, we were told by another official that chemistry deficiencies are generally not discussed over the telephone with sponsors. Two drugs we reviewed involved chemistry deficiencies which the chemist and the supervisory chemist stated could compromise patient safety. Other FDA officials, however, did not believe that initial clinical testing should be delayed until these deficiencies could be resolved by the sponsor. We could find no evidence that these deficiencies were discussed with the sponsor prior to receiving the deficiency letter. These deficiencies were included in FDA deficiency letters issued after clinical testing had begun.

FDA HAS NO FOLLOWUP SYSTEM TO ASSURE THAT ITS CONCERNS ARE ADDRESSED BY SPONSORS

Except when the beginning of clinical testing has been delayed (clinical hold) to resolve safety issues, FDA allows clinical testing to proceed without following up to determine whether IND sponsors have complied with or responded to its recommendations. Generally, FDA has no direct communication with clinical investigators regarding clinical protocols; instead, it communicates its concerns to the drug sponsor. The director of the division responsible for reviewing anticancer drugs told us that his division does not have a good way of determining when sponsors respond and whether they have complied with FDA requests. He said that the division's management information system does not have this capability, and the reviewers' heavy workload prevents them from keeping track of what comes in. Although FDA must primarily rely on sponsors to communicate its concerns to clinical investigators, FDA should establish a followup system to assure that its recommendations are implemented. Otherwise, patients may be unnecessarily exposed to potential risks during drug testing.

For example, FDA advised NCI in a November 26, 1979, deficiency letter that, as the sponsor for one drug being tested, it

should perform electrocardiograms[2] and radionuclide studies[3] to monitor cardiotoxicity[4] and exclude patients with prior adriamycin treatment and heart disease. FDA did not follow up to determine whether these recommendations were carried out. In June 1981, when it began receiving reports of patients with cardiotoxicity problems, FDA found that protocols had not been changed to incorporate its concerns. The first reports of cardiotoxicity involved patients with prior adriamycin treatment. NCI did not issue a warning to its clinical investigators until June 1981 (more than 1-1/2 years after FDA's initial recommendation) to monitor cardiotoxicity. Although we did not attempt to quantify the extent of the problem, we noted that protocols were still being submitted to FDA as late as December 1982 without including requirements for such monitoring.

In the case of another drug being tested, NCI notified FDA on March 9, 1982, that several patients had experienced hyperglycemia.[5] NCI told FDA that it had requested all its clinical investigators to revise their protocols to monitor for this drug side effect. NCI did not send FDA a copy of the warning letter. Consequently, FDA did not know what protocol corrections were being required by NCI. Based on a review of protocols later submitted which did not include such monitoring, FDA sent NCI a deficiency letter on May 5, 1982, requesting that protocols be modified to exclude patients with diabetes and monitor for hyperglycemia. FDA also requested that consent forms include hyperglycemia as a drug side effect. NCI officials told us that clinical investigators were aware of this drug side effect but acknowledged that the documentation may not have been adequate.

FDA officials told us that they never know whether sponsors inform clinical investigators of FDA's concerns unless suggested changes warrant revisions to protocols and/or the sponsor voluntarily notifies them of the corrective action taken. One of these officials told us that they are not always certain that NCI provides clinical investigators with all the available animal (preclinical) study results on investigational drugs. For three of the six NCI-sponsored drugs we reviewed, clinical brochures provided to clinical investigators did not include some

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[2]A graphic tracing of the electrical impulses in the heart.

[3]A medical technique used to visualize the most sensitive tissues and organs within the body.

[4]A poisonous or harmful effect on the heart.

[5]An abnormally increased content of sugar in the blood.

preclinical study results which NCI had available. This information would have aided investigators in designing their protocols for human testing. In two cases NCI did not inform clinical investigators of irreversible toxicities found in animals. In another case NCI did not inform investigators that test animals did not completely recover from toxicities caused by the drug. Consequently, clinical investigators did not know that they should monitor for these potential toxicities during drug testing. Although NCI complied with the FDA recommendations by updating its clinical brochures with this information, in the meantime patients may have been subject to unnecessary risks. An NCI official advised us that NCI now routinely provides all phase I investigators with reports on preclinical studies.

FDA DOES NOT ALWAYS RECEIVE AND PROMPTLY REVIEW IND AMENDMENTS

Sponsors do not always submit IND amendments to FDA for review, and when submitted, FDA frequently does not review them in a timely manner and sometimes does not review them at all. The amendments can include protocols for additional clinical studies. Review of IND amendments is particularly important for protocols on studies initiated after the initial IND is approved because amendments can significantly change a study and without review FDA cannot determine whether it has any safety concerns and whether patients are adequately protected.

Sponsors are required to approve protocols which amend the clinical studies. FDA's IND regulations[6] are unclear as to whether sponsors must submit protocols to FDA for clinical studies starting after the IND was approved. NCI officials said that although not required to do so by FDA regulations, they voluntarily submit protocols on new studies under approved INDs to FDA for its information.

IND amendments may include newly proposed clinical protocols, sponsor changes to ongoing clinical studies, sponsor progress reports, or ADR reports. These documents provide FDA with information on patient eligibility criteria, drug dosage levels, methods of drug administration, toxicities, and drug side effects, all of which significantly affect patient safety.

During our review we found 12 protocols involving 5 of the drugs included in our review that had not been submitted to FDA before clinical testing began. Only after receiving ADR reports did FDA realize that some of these protocols had not been submitted. For one drug being tested, FDA learned after receiving

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[6]See 21 C.F.R. 312.1(a)(2),(a)(12),(a)(13)(1982).

a report on the death of a patient that testing was being performed under a protocol that had not been submitted for review. NCI received this protocol on September 3, 1981, and clinical testing began in October 1981; however, FDA did not receive the protocol until December 2, 1981. An NCI official explained that NCI had not sent these protocols to FDA earlier because of an oversight.

Human testing of another drug began at one institution under three protocols before FDA or NCI could review them. Testing under one of these protocols began on June 9, 1980, but NCI did not receive the protocol for review until August 25, 1980. An NCI official told us that NCI gave oral approval to start testing in January 1981. The clinical investigator completed testing under this protocol on May 1, 1981. NCI submitted the protocol to FDA on June 5, 1981.

An NCI official told us that NCI became aware, based on an inspection at this institution, that testing had begun under several protocols before NCI had approved them. NCI requested the institution to stop testing on all protocols until it could determine what other studies had begun without its approval. The NCI official told us that NCI no longer gives oral approval. Clinical investigators now must receive written NCI approval to start testing under a protocol.

Even when sponsors submit IND amendments, FDA frequently does not review them promptly and sometimes does not review them at all. We reviewed 186 IND amendments and found 44 took 30 days or more to be reviewed while 48 showed no evidence of ever having been reviewed. This occurs because (1) reviewers are assigned a heavy workload and review of IND amendments is given a low priority and (2) IND amendments are frequently misfiled and not distributed promptly to reviewers.

For the years 1980-82, FDA received a yearly average of 4 new drug applications, 57 new drug application supplements, 74 INDs, and hundreds of IND amendments concerning anticancer drugs for review. As of March 1983, full-time professional staff primarily responsible for reviewing these documents consist of three medical officers, three pharmacologists, and two chemists. These reviewers also have responsibility for reviewing anti-inflammatory drug products. The reviewers not only are assigned new applications received by FDA, but also have an ongoing responsibility for active new drug applications and INDs assigned to them in prior years. For example, an FDA official stated that pharmacologists within the division are currently responsible for an average of 305 active INDs. FDA reviewers are also responsible for reviewing progress reports on marketed drugs,

handling safety problems with approved drugs, providing assistance on drugs from other divisions, responding to congressional requests, attending meetings, and conducting special studies.

Although IND amendments comprise the largest percentage of workload volume, other work is assigned a higher priority to comply with regulations and internal management deadlines. FDA reviewers have expressed concern about the heavy workload, complaining that they have insufficient time to carry out their responsibilities. For example, one FDA reviewer told us that many times he can make only a cursory review of IND amendments.

According to FDA officials, the agency also lacks sufficient administrative staff to process IND documents promptly. Delays in distributing and filing IND amendments hamper FDA's review process. Frequently, IND amendments are misfiled and require considerable time for FDA officials to locate. During our review we frequently encountered problems in locating documents related to individual INDs. In many cases IND material either had not been filed, taken from the file room without being signed out, found in the office of a reviewer, or just mislocated. FDA officials we spoke with agreed that there are problems and delays throughout the system for processing documents from the mailroom to the reviewers. They explained that there are an insufficient number of employees to handle this responsibility.

In one document delay, for example, FDA received an IND amendment dated December 31, 1981, on January 8, 1982, which included seven protocols that had been revised to incorporate restrictions to monitor for cardiotoxicity. However, the medical officer responsible for this drug did not receive this amendment until February 18, 1982, at which time he completed his review and concluded that several protocols did not include all the required restrictions outlined in NCI's warning letter to its investigators. FDA sent NCI a deficiency letter on June 3, 1982, requesting that the corrections be made. FDA officials could not explain why it took 3-1/2 months to send this deficiency letter. However, as previously explained, FDA has generally been slow in sending deficiency letters because of delays in completing written reviews, a heavy workload, and insufficient staff to carry out its functions.

In the case of another drug being tested, FDA received an IND amendment dated December 1, 1981, on December 2, 1981. The FDA medical officer did not receive this amendment until February 8, 1982, more than 2 months later. He completed his review on February 11, 1982, and concluded that two protocols should be revised so that children and adults are not enrolled in the same phase I study. FDA did not send NCI a deficiency

letter requesting changes to this protocol until March 16, 1982, 3-1/2 months after the amendment was received by FDA.

CONCLUSIONS

FDA appears to lack sufficient staff resources to assure that patients are adequately protected during anticancer drug testing. FDA's apparent insufficient staffing coupled with a heavy workload hampers FDA's review of initial INDs and amendments to INDs. In its proposed budget for fiscal year 1984, FDA has proposed reallocating 35 staff years from other programs to drug approval. While we have not reviewed these other programs to know the effect the loss of staff will have, we believe that the proposed change if implemented, will help to improve FDA's reviews of investigational new anticancer drugs.

FDA appears to conduct safety reviews of INDs in a timely manner, but documentation showing that reviews were completed is not always available even though FDA requires it. We believe that FDA should assure that this written documentation is prepared so that it could verify that the review was completed within the initial review period. We also believe that all safety concerns raised by FDA reviewers, whether they are serious enough to warrant putting a hold on the studies or not, should be brought to the attention of sponsors before clinical testing begins.

Regulations should be clarified to require that proposed protocols for all clinical studies be submitted to FDA before drug testing begins. Without examining all the protocols, FDA cannot assure that patients will be adequately safeguarded. Inadequate followup action also prevents FDA from determining whether sponsors have responded to FDA's concerns. FDA lacks a formal mechanism that would enable it to follow up on its recommendations in a timely manner.

RECOMMENDATIONS TO THE SECRETARY OF HHS

We recommend that the Secretary direct the Commissioner of FDA to:

--Require that IND reviewers document for the record, within 30 days of the date an IND is submitted to FDA for initial review, that they have satisfied themselves as to the safety of patients participating in tests of new anticancer drugs.

--Require that IND reviewers whenever practical discuss all IND deficiencies with sponsors before clinical

testing begins, or promptly after a deficiency is noted if testing has already begun, and then communicate all such deficiencies in writing to the sponsor in a timely manner. To deal with situations where this procedure is not practicable, guidance should be developed to assist FDA reviewers in determining which deficiencies are sufficiently significant to be communicated promptly to test sponsors.

--Establish a formal followup system so that FDA can know whether IND sponsors respond to its recommendations to improve patient safety.

--Revise its regulations to require sponsors to approve and submit for FDA review, before clinical testing begins, all clinical protocols.

--Develop a system for identifying major IND amendments and promptly distributing them to reviewers.

We also recommend that the Secretary require the Director of NCI to advise FDA in a timely manner of actions taken or to be taken on concerns raised by FDA during its review of NCI's IND applications.

AGENCY COMMENTS AND OUR EVALUATION

In commenting on a draft of this report, HHS made an overall comment that the report could appear to incorrectly imply that cancer patients are being exposed to unnecessary risks based on procedural deficiencies. HHS said that procedural deficiencies that could or might imply risk do not establish risk. We agree that such a distinction is useful and valid. However, certain of the deficiencies we identified, such as FDA's not reviewing new protocols before testing begins and not assuring that its concerns have been addressed by test sponsors, could have the potential of exposing patients to unnecessary risks. In commenting on our specific recommendations, HHS agreed that there is a need to ensure that IND reviewers document within 30 days of the date an IND is submitted to FDA that they have satisfied themselves as to the safety of patients participating in tests of new anticancer drugs. HHS stated that current policy requires such documentation from each of the three disciplines (medical officer, pharmacologist, and chemist), not only for anticancer drugs, but for all drugs. HHS agreed to examine the extent to which this problem exists regarding anticancer drugs by surveying the files for signed 30-day review forms. FDA plans to issue a memorandum emphasizing the need for prompt processing of review forms by reviewers and expedited handling by document personnel.

HHS disagreed with our recommendation that IND reviewers discuss all IND deficiencies with sponsors before clinical testing begins and then communicate all such deficiencies in writing to the sponsor promptly. HHS stated that currently reviewers are responsible for identifying when an IND has critical deficiencies that necessitate its being placed on hold until the deficiencies are corrected. HHS does not believe that it is necessary to immediately discuss with the sponsor deficiencies that do not significantly affect the safety of the planned study or its likely usefulness. HHS stated that FDA's current practice is to promptly transmit critical deficiencies.

We continue to believe that in addition to advising sponsors of safety concerns which could result in delaying the start of clinical testing, FDA should also notify sponsors of other concerns which the sponsor should address. Based on the time required by FDA to send deficiency letters, sponsors could have clinical testing underway for 4 months by the time they become aware of these other deficiencies. We do not believe that it would require much additional effort for FDA to discuss these other issues when it notifies the sponsor of what FDA classifies as critical issues. For the 10 drugs in our review, the additional deficiencies identified could have been discussed in a brief telephone conversation. Because there could be instances where it is not practicable to discuss all deficiencies, we have revised our recommendation to provide that a definition of deficiencies sponsors should be made aware of promptly be developed. The significance of this issue would be reduced if FDA sent deficiency letters to the sponsors promptly.

On our recommendation that FDA establish a formal followup system so that FDA can know whether IND sponsors respond to its recommendations to improve patient safety, HHS advised us that while it would appear to be useful to have a mechanism for ascertaining whether sponsors have responded to all deficiencies, the need for a system as a supplement to the continued monitoring by reviewers has not been demonstrated. HHS said it will, however, consider whether this is a problem and whether there is a reasonable way to do this within the limits of available resources.

We believe the need for such a system has been demonstrated. As previously indicated on pages 12 to 14, we found examples where sponsors had not notified FDA of what action they had taken or would take on its recommendations, and FDA officials told us that they are not always certain what actions sponsors have taken.

HHS agreed with our recommendation that FDA revise its regulations to require sponsors to approve and submit all clinical protocols to FDA for review before clinical testing begins. HHS stated that it will soon propose new IND regulations that will explicitly require sponsors to submit new protocols before beginning clinical testing using the new protocols.

HHS also agreed with our recommendation to develop a system for identifying major IND amendments and promptly distributing them to reviewers. HHS stated that its proposed new IND regulations will require the sender to identify and separate protocol amendments from information amendments. This will allow the protocol amendments to be handled expeditiously.

HHS did not agree with our recommendation that NCI be required to advise FDA in a timely manner of actions taken or to be taken on concerns raised by FDA. HHS stated that it was not necessary to impose any requirements in this regard because NCI has responded promptly to FDA concerns and will continue to do so. Since we found instances where NCI had not advised FDA promptly of what action, if any, it would take on FDA concerns, we believe that a specific requirement for NCI to respond promptly to FDA's concerns would be helpful.

CHAPTER 3

CLINICAL TESTING GENERALLY CONDUCTED IN ACCORDANCE WITH FDA AND NCI REQUIREMENTS, BUT IMPROVEMENTS CAN BE MADE

When conducting clinical tests with investigational drugs, sponsors, clinical investigators, and institutions have responsibilities relating to patient informed consent, protocol compliance, and ADR reporting. Our review of a sample of 10 investigational new anticancer drugs showed that these responsibilities were generally, but not always, being carried out in accordance with applicable FDA and NCI requirements.

At two institutions, the informed consent process did not always comply with FDA regulations. One institution did not always use the most recently updated forms, and the IRB did not ensure that consent forms fully complied with FDA regulations. Clinical investigators appeared to be complying with their approved study protocols to a satisfactory degree regarding patient eligibility and testing requirements. While ADR reporting has improved, the reporting of serious adverse reactions was not always prompt. The definition of "adverse reaction" remains vague and somewhat subjective, and FDA regulations (21 C.F.R. 312.1(a)(12), (a)(13)(1982)) do not contain specific reporting time frames.

Both sponsors and clinical investigators appeared to exhibit therapeutic intent--attempting to help patients rather than merely gathering scientific data--in carrying out phase I clinical trials with anticancer drugs. However, few patients actually benefit from phase I testing, and as discussed on pages 31 and 32, estimates prepared by NCI of patients benefiting from such testing can be misleading.

INFORMED CONSENT PROCESS GENERALLY COMPLIED WITH

The informed consent process was generally carried out in accordance with FDA regulations. Of the 171 patient files[1] at the seven institutions we checked for informed consent forms, only 1 file was missing the form. In this case, the clinical investigator could not explain why the form was missing, but

[1]The 171 patient files were selected from studies involving 8 of the 10 drugs in our sample. We did not obtain permission from two of the private drug sponsors to review patient files.

insisted that an informed consent form must be signed by each patient before he would administer the drug.

At another institution we found four cases in which the clinical investigators had used patient consent forms that had not been updated with the most recent toxicity information. (The drug in question had been found to contain a risk of cardiotoxicity.) The clinical investigator in three of these cases explained that the forms used were probably the only ones available in the clinic when patients were admitted and that the risks of cardiotoxicity had been orally explained to the patients.

Although not required to do so by Federal regulations, FDA reviews selected informed consent forms when they are submitted with INDs and IND amendments. FDA found that two IRB-approved consent forms for drugs included in our sample did not contain everything required by FDA regulations (21 C.F.R. 50.25, 50.27 (1982)). The omitted information included certain risks and potential benefits related to the drugs.

The extent to which patients and their families must understand the risks of their participation in drug studies is a controversial subject. Informed consent is a particularly difficult issue when it involves terminally ill cancer patients. Since these patients are in a desperate situation, it is thought by some that they either may be vulnerable to a physician's influence or may be unable to understand all the implications of their decision. Some patients may not want to know all the details of the possible side effects of the drug, while other patients may want all the information they can get. In any event, the patient's physician has the obligation to ensure that the patient knows the risks of taking the drug, the benefits that may be available, and that participation in the drug testing is voluntary and can be terminated at any time.

Informed consent is not simply a sheet of paper signed by the patient; rather, it is an ongoing process which involves continuing discussions between the patient and the physician. We could not verify what transpired during these sessions and, therefore, could not assess their adequacy.

An important aspect of informed consent consists of the forms and information required by FDA regulations for all patients undergoing treatment with an investigational drug. The regulations require that the informed consent forms include:

1. A statement that the study involves research, an explanation of the purposes of the research and the expected duration of the patient's participation, a

description of the procedures to be followed, and identification of any procedures which are experimental.

2. A description of any reasonably foreseeable risks or discomforts to the patient.

3. A description of any benefits to the patient or to others which may reasonably be expected from the research.

4. A disclosure of alternative procedures or courses of treatment, if any, that might be advantageous to the patient.

5. A statement describing the extent to which patient records will remain confidential.

6. An explanation for research involving more than minimal risk, as to whether any compensation or medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained.

7. An explanation of whom to contact for answers to pertinent questions about the research and the research patients' rights.

8. A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the patient is otherwise entitled, and that the patient may discontinue participation at any time without penalty or loss of benefits.

While the clinical investigator has the responsibility to provide this information to the patient, an IRB (see p. 4) has the responsibility of reviewing the informed consent form and of recommending additions or changes to the form if, in the IRB's judgment, the protection or welfare of patients would be enhanced by such action. Regulations do not require that consent forms be sent to FDA for review (21 C.F.R. 50(1982); 21 C.F.R. 312.1(a)(1982)).

CLINICAL INVESTIGATORS GENERALLY COMPLYING WITH PROTOCOL REQUIREMENTS

Clinical investigators appeared to be complying to a satisfactory degree with their approved protocols regarding patient

eligibility and testing requirements. Although some deviations occurred, they were generally explained satisfactorily by the investigator.

Before a clinical study begins, a drug's sponsor is required to submit the clinical investigator's plan of investigation (or "protocol") to FDA for review (21 C.F.R. 312.1(a)(2) 10(1982)). The protocol may include reasonable alternatives and variations and should be supplemented or amended when any significant change in direction or scope of the investigation is undertaken. Investigators must use their protocols (along with any amendments) as guidelines for their clinical tests.

In our review of data from eight of the drugs included in our review, we compared patient eligibility criteria and patient testing requirements as stated in the study protocols with data in the patient files. We reviewed a sample of 171 patient files at seven institutions. While 134 patients met eligibility requirements, 37 did not. Clinical investigators provided us with adequate explanations for allowing 31 of these ineligible patients to participate in the drug studies.

For example, one institution allowed 5 patients with functional capacity scores[2] (a criterion listed in the protocol) lower than provided for in the protocol to receive the investigational drug. The investigator explained that he had decided, with NCI's knowledge, not to deny patients the drug on the basis of a lowered functional capacity, since (1) the functional capacity assessment for measuring a patient's ability to remain alive for the course of the drug treatment is imprecise and subject to differing interpretations by different physicians and (2) the patients involved, who were only one grade below the functional capacity cutoff, had been promised the drug, having previously met eligibility criteria. An investigator who commented on protocol adherence stated that no protocol can ever be completely followed. Other investigators indicated that flexibility is necessary in interpreting protocols, since individual cases sometimes demand individualized medical judgment.

Although laboratory tests were not always performed on patients to the extent called for by the protocols, we found that investigators substantially complied with protocol requirements. We found that 48 of the 171 patients did not receive all the required tests. Clinical investigators adequately explained to us

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[2]A subjective numerical rating from 0 to 5 (e.g., 0 = fully active; 5 = dead) used in an attempt to determine whether a patient's life expectancy will at least equal the minimum necessary time period for a full course of the drug.

the reasons for these omissions in 38 cases. Among the reasons given for the absence of certain tests for the patients were (1) patients sometimes did not keep appointments; (2) patients did not feel well enough to have tests done at the intervals specified by the protocols; (3) tests were done, but the information was misplaced; and (4) tests were apparently ordered, but were not done.

CLINICAL INVESTIGATORS AND DRUG SPONSORS DO NOT ALWAYS PROMPTLY REPORT ADRS

According to an FDA official, while adverse reaction reporting has improved since the 1981 congressional hearings, problems still exist in this area. The lack of specific time frames for ADR reporting and the lack of a clear, generally agreed upon definition of a reportable adverse reaction in the regulations[3] may be contributing to the untimely reporting, or the nonreporting, of such reactions. In addition, when ADRs are reported, FDA does not always promptly review them.

ADR reporting problems-- specific examples

Of the 10 drugs reviewed, we found problems in ADR reporting with 5 drugs. Three of the five were NCI-sponsored drugs; the other two were privately sponsored. The ADR reporting problems on two of the NCI drugs occurred before the start of NCI's 1981 effort to improve its ADR reporting.

One of the NCI drugs was an analogue (similar chemical structure) of a known cardiotoxic drug, and FDA had recommended earlier that NCI instruct its investigators to monitor for cardiotoxicity. However, when investigators started submitting reports of cardiotoxicity, NCI delayed sending them to FDA because of uncertainty over whether the reactions were drug related. An FDA medical reviewer later emphasized that NCI should report serious reactions immediately and that such reports should not be delayed while a sponsor determines the reaction's relationship to the drug. NCI did eventually notify all investigators of these adverse reactions and recommended that all patients be carefully monitored for cardiotoxicity, but this action was taken more than 1-1/2 years after FDA initially recommended it. By that time, NCI had received nine reports of cardiotoxicity. We also found that several months after NCI notified the investigators, one clinical investigator did not submit reports of cardiotoxicity because of doubt that this reaction was drug related.

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[3]See 21 C.F.R. 312.1(a)(2),(a)(6),(a)(13)(1982).

In the case of another drug being tested, NCI did not report an adverse effect to FDA because its Adverse Drug Reaction Committee concluded that it was not drug related. We noted, however, that NCI reported to FDA several other non-drug-related events for this drug. A patient experienced cardiotoxicity 11 days after receiving one drug treatment and later refused further treatment. The clinical investigator reported it as possibly drug related, but NCI's Adverse Drug Reaction Committee concluded it was not caused by the drug. NCI's drug monitor told us that based on this conclusion, there was no need to report it to FDA. He said that NCI is not required to report non-drug-related events to FDA. However, the FDA medical officer responsible for this drug told us that all toxicities that occur during the testing of investigational drugs must be reported to FDA so that a fair assessment can be made on the safety of the drug.

For another of its drugs, NCI was not prompt in sending some ADR reports to FDA. In two cases of severe thrombocytopenia (a decrease in the number of blood platelets, which is an expected reaction from this drug), the report was submitted to NCI by the clinical investigator on June 29, 1982. FDA did not receive the report from NCI until August 3, 1982. An NCI official stated that these were known reactions and were not alarming.

Each of the two privately sponsored drugs had only one reported ADR at the time our review was completed. In one case the ADR involved a severely decreased white blood count which, according to the firm, may have contributed to the patient's deteriorating condition and subsequent death. The investigator took almost 2 months to report the reaction to the sponsor; this accounted for most of the delay in reporting to FDA. An FDA reviewer mentioned that this sponsor has had timeliness problems in the past but has agreed to correct them.

The one ADR reported for another privately sponsored drug was submitted to FDA over 2 months after it was first reported to the sponsor, largely because of miscommunication between the sponsor and the investigator. The ADR involved a death, but its relationship to the drug was uncertain. The investigator stated that when the ADR was reported to the sponsor by telephone, the sponsor apparently made no record of the telephone conversation and did not send a report to FDA. Several weeks later, the investigator submitted a written report to the sponsor, who then reported it to FDA.

While sponsors have sometimes been late in reporting ADRs, we found indications that FDA has not been prompt in performing its reviews of the ADRs when they are received. We found eight

instances where FDA did not review ADRs for days or weeks after they were submitted. For example, FDA received ADRs from NCI on March 9 and 30, 1982. These ADRs were not reviewed by the medical officer until August 11, and September 16, 1982, respectively. As discussed on page 16, the system for document flow in FDA appears to be a major reason why ADRs are not forwarded promptly to reviewers and, hence, why review of ADRs is late. While ADR reports should be given priority over other incoming documents, the reports are mixed in with other correspondence and are not always recognized as priority documents by distribution system personnel.

Problems in defining ADRs

The task of defining ADRs for investigational cancer drugs is a difficult one. Due to the unique, highly toxic nature of most of these drugs and the physical toll taken on cancer patients by the disease itself, determining whether a cause and effect relationship exists between the drug and a patient's reaction is not easy. The reporting system must rely on the clinical investigator's ability to correctly make the connection between the drug and the reaction. Although FDA regulations (21 C.F.R. 312.1(a)(6),(a)(13)(1982)) contain requirements on reporting of ADRs, wording regarding the definition of an ADR is vague and nonspecific. According to FDA regulations, the clinical investigator has the following responsibility regarding ADRs:

> "Any adverse effects that may reasonably be regarded as caused by, or probably caused by, the new drug shall be reported to the sponsor promptly, and if the adverse effect is alarming, it shall be reported immediately."

The sponsor, in turn, has the following responsibility:

> "The sponsor shall promptly investigate and report to the Food and Drug Administration and to all investigators any findings associated with use of the drug that may suggest significant hazards, contraindications, side effects, and precautions pertinent to the safety of the drug. If the finding is alarming it shall be reported immediately and the clinical investigation discontinued until the finding is adequately evaluated and a decision reached that it is safe to proceed."

The words "alarming" and "significant" do not provide very definite guidance about specific types of reactions that should

or should not be reported. Such vagueness contributes to investigators having varying interpretations of what an ADR is and using varying reporting criteria. On the other hand, devising a precise definition to fit all types of drug tests being done would be difficult. While too narrow a definition might exclude ADRs that should be reported, too broad a definition could result in FDA being inundated with possible ADRs, obscuring the identification of important ADRs.

When we asked investigators to comment on their definition of a reportable ADR, they generally categorized ADRs as unexpected reactions and reactions which may be expected, but which occur with unexpected severity. In practice the variables in specific cases and the investigators' subjectivity can result in differing interpretations of similar information.

A further element complicating the decision as to whether an ADR should be reported is the relationship of the reaction to the drug in question. Investigators often find the relationship between the reaction and the drug to be uncertain. According to one investigator, unless the adverse reaction occurs right after the drug's administration, the cause/effect relationship can be difficult to determine. Both sponsors and investigators have delayed reporting some patient reactions to determine whether or not they are drug related.

FDA regulations do not provide specific guidance for the timely reporting of ADRs. The word "promptly" gives no indication as to an actual reporting time frame. FDA has traditionally advocated a 15-day time frame for reporting ADRs to them, although this time frame is not written in the regulations. In February 1983, the Secretary of HHS proposed strengthening requirements for ADR reporting to FDA by requiring specific time frames for reporting fatal or life-threatening reactions. After review by the Office of Management and Budget, the proposal will be published in the Federal Register as part of a proposed rule.

NCI's ADR reporting procedures

As the sponsor of many anticancer drugs, NCI began in 1981 to devise its own requirements which more specifically define what an adverse reaction is and when an investigator should report it. According to NCI's most recent (January 1983) ADR reporting guidelines, each investigator engaged in clinical research with NCI-supplied investigational drugs is responsible for promptly reporting ADRs to NCI's Division of Cancer Treatment. The division's policy is to encourage investigators to submit such reports even if there is only a suspected drug effect. After review by a drug monitor, the reports are submitted to NCI's Adverse Drug Reaction Committee.

These guidelines require that initial notice of a serious ADR be called in to the Division's Investigational Drug Branch. As a followup, a written report (on FDA form 1639) should be sent within 10 working days to the branch. More specifically, serious, life-threatening reactions and lethal toxicities to major organs should be reported even if previously reported in the clinical brochure, in the annual report and/or in the literature; life threatening and lethal myelosuppression[4] in solid tumor patients should be reported only if unexpected and if clearly related to the experimental drug; and lethal aplasia[5] in leukemia patients should be reported only if clearly related to the experimental drug.

The guidelines also require that other ADRs (that are not characterized as serious) be reported promptly in writing (on FDA form 1639) if that type of effect has not previously been reported in the clinical brochure, annual report and/or the literature. For example, if a patient develops dermatitis suspected to be related to an investigational drug, and dermatitis is not indicated in the clinical brochure or in the annual report, a report should be sent to the Investigational Drug Branch within 10 working days of its occurrence.

NCI documents show that it had increased reporting of ADRs to FDA from 83 in 1981 to 181 in 1982.

THERAPEUTIC INTENT MAY BE PRESENT IN PHASE I TESTING BUT FEW PATIENTS BENEFIT

Some medical experts have questioned whether therapeutic intent (i.e., the intention to help a patient) as opposed to merely gathering scientific data actually exists during phase I testing of cytotoxic anticancer drugs. Our discussions with NCI, FDA, and medical investigators and a review of the results of phase I studies of cytotoxic anticancer drugs indicate that therapeutic intent is present in phase I. However, only a small percentage of patients make significant gains against their diseases in phase I trials.

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[4]Myelosuppression is defined as inhibited bone marrow activity, resulting in decreased production of blood cells and platelets.

[5]Aplasia is defined as the lack of development of an organ or tissue, or of the cellular products from an organ or tissue.

Therapeutic intent important in phase I cancer drug tests

Therapeutic intent is not an issue with most phase I experimental drug studies (other than anticancer drugs) because the humans taking the drugs are not ill and, therefore, do not need help. In fact, FDA regulations (21 C.F.R. 312.1(a)(2)10.a(1982)) do not mention therapeutic intent as a purpose of phase I studies.

The cytotoxic effects of anticancer drugs make them different from most other drugs. Because experimental cytotoxic anticancer drugs are highly toxic with potentially dangerous side effects, they can ethically be given only to severely ill cancer patients. These patients desperately need help, and therefore, the issue of therapeutic intent becomes important. According to an NCI official, giving dangerous experimental drugs to seriously ill patients merely to obtain scientific data would not be morally justifiable.

Investigators claim therapeutic intent present

Physician-investigators we met with stated they would not administer an experimental cytotoxic anticancer drug to a patient unless they thought the patient could be helped by the drug. Of the 136 phase I patient files reviewed, we found only one case where a patient was given an experimental anticancer cytotoxic drug that the investigator did not believe could help the patient. In this case he had been eligible for and was promised the drug. His physical condition deteriorated to the point where he had only a few days to live. The drug was administered with little hope of positive results because the physician did not want to destroy the patient's hope in his last few days.

An HHS task force, formed by the HHS Assistant Secretary for Health in October 1981 to assess FDA and NCI administration of anticancer drug studies, stated in their January 1982 report that the medical community believes therapeutic intent in phase I anticancer drug studies is demonstrated by:

--Humans being recruited into protocols only if they are terminally ill and conventional treatment has failed.

--Drugs being used only after animal testing has shown evidence of anticancer activity and review has deemed a drug to be promising.

--Findings of an NCI study that 9.5 percent of patients in NCI phase I drug studies from 1975 to 1980 showed a response to their treatment.

Few patients benefit from phase I tests

In response to a request from the HHS task force, NCI reviewed the results of phase I drug testing from 1975 to 1980 and found that 9.5 percent of patients in phase I studies responded to treatment. We believe that this figure is somewhat misleading because it implies about a 1 in 10 chance of real patient benefit. An examination of the response rate data showed that the number of patients benefiting significantly was much less.

NCI broke down patient responses into three classes--minor, partial, and complete. Almost half the patients with responses (4.1 percent) were classified as having minor responses--meaning, according to one NCI official, that the drugs had a small, medically insignificant effect on the patients' cancer. About 2.9 percent had a partial response--meaning the drugs reduced their measurable cancer by 50 percent or more. Another 2.5 percent had a complete response--meaning their cancers, at least temporarily, disappeared completely. Overall, therefore, using the NCI data the percentage of patients significantly benefiting was about 5 percent.

More recent data from late 1979 through October 1982 showed lower percentages of patients benefiting. The overall response rate was 6 percent, of which 3.3 percent were minor responses. Partial and complete responses were 2.2 and 0.5 percent, respectively, for a total 2.7 percent of patients significantly benefiting from phase I drugs.

The more recent data showed 3 of 37 drugs accounted for 91 percent of the complete responses and 61 percent of the partial responses. Also, 91 percent of the complete responses and 24 percent of the partial responses occurred in only one type of cancer--leukemia.

An NCI official said only a small percentage of patients benefit significantly from phase I studies because (1) most patients entering phase I studies have advanced cancers; (2) prior drug treatment, which most patients entering phase I have had, makes their cancers less sensitive to further drug treatment; and (3) the majority of drugs tested in phase I studies do not ultimately prove effective.

Leukemia patients more often benefit in phase I studies, according to this official, because leukemia is the most drug-sensitive type of cancer.

CONCLUSIONS

The informed consent process at the institutions we visited was generally carried out according to FDA regulations. The minor problems we found generally related to the unavailability of recently updated consent forms at one institution and the inadequate review of informed consent forms by an IRB.

For the most part, investigators at the institutions where we reviewed patient files appeared to be following their protocols. When deviating from protocol eligibility guidelines, investigators appeared to be acting in what they believed to be the patients' best interests. Investigators generally gave adequate explanations when patient laboratory test results were missing from the files. The number of tests not performed or documented did not appear to be excessive and patient safety did not appear to have been compromised.

While procedural mechanisms exist to deal with ADRs at both the FDA and sponsor levels, reporting of ADRs to FDA from drug sponsors, and sometimes to drug sponsors from clinical investigators, could be more timely. Late reporting, in addition to being caused by inattention by investigators and insufficient monitoring by sponsors, could be due partly to the vague definition of ADRs in FDA regulations, the absence of a time frame for ADR reporting in the regulations, and confusion as to what extent reactions of questionable relationship to the drug should be reported. An FDA official advised us that the agency has proposed changes in the IND regulations which would establish specific time frames for ADR reporting.

FDA could improve the promptness with which it reviews ADRs by requiring that sponsors label or otherwise highlight ADR forms or mailing envelopes. This would help ensure that ADRs are recognized and dealt with in a more timely manner.

Therapeutic intent appears to be present in phase I studies of cytotoxic anticancer drugs, but few patients significantly benefit from these studies. According to NCI officials, few benefit because their diseases are usually far advanced by the time they get to phase I studies and most experimental drugs tested in phase I do not ultimately prove to be effective.

RECOMMENDATIONS TO THE SECRETARY OF HHS

We recommend that the Secretary require the Commissioner of FDA to:

--Give sponsors and clinical investigators more precise guidance as to what types of reactions they should report as ADRs and when they should report possible ADRs in cases in which the reaction's relationship to the drug is uncertain. This should include specific time frames for reporting ADRs to FDA.

--Urge sponsors, if they have not already done so, to establish definite time frames for clinical investigator reporting of ADRs which will allow the sponsors time to meet FDA's reporting requirements.

--Instruct sponsors to label or otherwise highlight ADR forms or mailing envelopes to ensure that ADRs will be recognized and dealt with immediately upon their arrival at FDA.

AGENCY COMMENTS AND OUR EVALUATION

HHS stated that the new IND regulations that FDA will propose will clarify requirements for submitting ADR reports and set forth specific time frames for the submissions. The new regulations will also require that reports of serious adverse effects be prominently identified for expeditious handling by FDA. HHS also stated that current regulations require that investigators promptly inform sponsors of adverse effects. This requirement is also contained in the forms signed by the investigators as part of their IND agreements.

Since HHS did not provide access to the proposed regulations, we could not determine whether the proposed changes will give sponsors more precise guidance on what types of reactions to report. Regarding our recommendation that specific time frames be established for investigators to report ADRs to sponsors, neither the current regulations nor the forms signed by the investigators provide specific time frames for ADR reporting. We continue to believe that specific time frames should be established.

CHAPTER 4

NEED TO IMPROVE MONITORING OF CLINICAL TESTING

Although various aspects of NCI and FDA clinical drug study monitoring appear to be adequate, both agencies could make improvements affecting this vital check on patient safety. FDA should finalize its proposed regulations on drug sponsor monitoring responsibilities and establish regulations to standardize drug sponsor annual reporting requirements. NCI should (1) obtain more complete and timely input for its phase I drug study data base from clinical investigators, (2) ensure that all of its clinical drug studies are properly monitored, and (3) improve its drug accountability controls over clinical investigators.

MONITORING REQUIREMENTS AND PROCEDURES

Monitoring of clinical studies is performed by FDA, drug sponsors (NCI and private companies), and IRBs. The extent and type of monitoring done by these groups varies as explained below.

FDA

In accordance with its regulations,[1] FDA's drug test monitoring involves reviewing (1) ADR reports submitted by sponsors as they occur and (2) progress reports submitted by sponsors at intervals not exceeding 1 year. In addition, FDA reviews IND amendments submitted by sponsors and performs some onsite monitoring of IND clinical studies. FDA also makes onsite visits to institutions to monitor IRB activities and determine whether IRBs are complying with its regulations.

Drug sponsors

FDA regulations require sponsors to monitor the progress of clinical drug studies and evaluate evidence obtained from investigators about the safety and effectiveness of the drugs. The current (as of March 1983) regulations are not specific regarding (1) how drug sponsors should perform their monitoring responsibility and (2) how frequently monitoring should be done.

NCI's monitoring system, as of March 1983, includes in-house monitors, a private contractor, peer reviews, and meetings

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[1]21 C.F.R. 312.1(a)(5),(a)(12),(a)(13)(1982).

with investigators. NCI's in-house monitors are assigned to follow individual clinical drug studies primarily through telephone and mail contact with the clinical investigators. NCI uses a private contractor to make site monitoring visits on its phase I and some early phase II cytotoxic drug studies. The contractor also collects data, maintains a computerized data base, and prepares computerized reports on these studies. NCI uses a peer review monitoring system for its cooperative study groups[2] engaged in phase II and III clinical drug studies. In the peer review system, investigators make site visits to monitor the performance of other investigators in accordance with NCI's guidelines. In addition, NCI holds several meetings each year where investigators studying the same drugs report on the results of their work and share information.

Private company drug sponsors indicated that they closely monitor drug trials through data collection and site visits. For example, one firm said its clinical research associates make site visits every 4 weeks during which drug accountability, protocol adherence, and data flow are verified. It said patients are not treated under the protocol until their eligibility has been reviewed by the sponsor. Another company stated that it reviews patients for eligibility before they are allowed to receive the drug. This company said it makes site visits at least yearly to compare data submitted by the investigator to patient records. The company stated that it will not ship the drug until it verifies that patients have signed consent forms. According to the company, drugs are shipped by return receipt mail. This company added that it also inspects and inventories drug supplies during site visits.

IRBs

IRBs are required by FDA regulations (21 C.F.R. 312.1(a)(2)10.c(1982)) to conduct continuing reviews of drug studies at their respective institutions at intervals not less than once a year. IRB responsibilities include review and approval of any changes to the research and review of unanticipated problems involving risks to patients or others.

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[2]Institutions which have combined with NCI funding to do clinical research on NCI-sponsored drugs. By cooperating they can apply the same drug study protocol to more patients than a single institution could.

INVESTIGATORS NOT SENDING COMPLETE OR TIMELY DATA TO NCI ON DRUG STUDIES

According to the NCI clinical studies monitoring service contractor's July 1982 annual report, only about half of the patient laboratory test data required by NCI's phase I drug protocols was being submitted by the investigators, and much of the data submitted was coming in significantly late. The report also shows that data submitted on some important items, such as patient eligibility, are frequently insufficient. Although a January 1983 report shows some improvement, further progress should be made to ensure that the data base provides an accurate, up-to-date overview of NCI's drug studies. NCI has recognized the need to improve investigators' data reporting to its contractor and is planning an experiment using computer terminals to improve the reporting.

The NCI clinical studies monitoring service contract was awarded in September 1979 for 3 years for $1,632,179. The original contract was extended until June 1983 when bids were to be accepted on a new contract. The contract is for (1) detailed data collection and reporting on individual drug studies; (2) maintenance of a computerized data base; and (3) site visit monitoring to verify reported data, examine facilities, and review procedures. The contract primarily covers NCI's phase I clinical studies although the site visit monitoring will be extended to include some phase II and III studies under the new contract.

The contractor's reports show data submitted by investigators to NCI's data base as of July 1982 were not complete or timely. For each drug study protocol, investigators submitted an average of 58 percent[3] of the laboratory test data required. Delays of 60 days or more occurred in submitting data for 41 percent of the drug studies. For 14 percent of the studies, investigators did not submit enough data to determine whether more than half the patients in each study were eligible to take drugs. As of January 1983, investigators had improved their reporting of laboratory test data from 58 to 60 percent. Delays of 60 days or more in reporting data still occurred in 37 percent of the studies versus 41 percent in July 1982. Also, the percentage of studies for which patient eligibility to take the drugs could not be determined for over half the patients remained the same--14 percent.

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[3]The percentage was computed by taking a simple average of the percentages of laboratory test data submitted for each study protocol. The computation was not weighted for differences in the number of tests required by each protocol.

An NCI official stated that these percentages make the data reporting situation look worse than it currently is because the contractor's reports from which they were taken show averages over the life of each protocol. The official said that long-term averages do not show what is happening now. The official had the NCI contractor prepare a special analysis of the data. The analysis, to eliminate the effects of long-term averages, took only those study protocols started in each particular year covered. The analysis showed, for those drug protocols started in the year ended March 31, 1983, the average delay in reporting data to NCI's contractor was 29 days, while 70 percent of the laboratory tests were done and enough data was submitted to judge the eligibility of 89 percent of the patients entered into these protocols. The official said this indicates that investigators are improving on their data reporting but agreed that there is still a need for better reporting.

NCI and data base contractor officials cited three causes for the missing data. First, investigators frequently include more patient testing requirements in drug study protocols than can actually be performed for all patients. Second, investigators simply fail to send in patient test results. Third, patients are not getting protocol-required tests because they drop out of the program or are too sick to have the tests done.

We could not determine the precise extent to which each cause was responsible for this problem, but as discussed in chapter 3, our review of a sample of eight drug studies did disclose instances where investigators were not sending complete data to the contractor. We found, however, in our sample that most protocol-required tests were being performed.

Reasons given by the contractor for the delays in submitting data included the fact that some investigators want to carefully review all data before forwarding it while others are inefficient in assembling data. Since investigators generally submit data to the contractor every 2 weeks, a 60-day lag, or even the 29-day average provided to us by an NCI official, appears to represent a significant delay.

NCI officials presented somewhat conflicting views on the usefulness of the data base reports and their accuracy. One drug monitor stated that the data base computer is inflexible and if only one small data item is missing, it will declare patients ineligible. He indicated he does not rely on the reports for patient eligibility information. He also stated that missing data is normal for these computer reports, and his primary source of drug study information is telephone contact with the investigators. This monitor's supervisor, however, stated that the computer data base is a vital part of the NCI drug study

monitoring program and is an excellent tool for performing data analysis which would otherwise be very time consuming. The supervisor noted that the monthly reports provide an excellent tracking device for study progress and ready reference when questions come up. The supervisor contended that virtually all missing data concern nonessential tests stemming mainly from drug protocols which require that some tests be performed at an ideal frequency which can not always be obtained.

Clinical investigators said they have little use for the reports they receive now. The reports each investigator receives cover only the investigator's specific work and therefore do not give the investigator any new information. The two investigators we asked said they would be interested in receiving reports which cover the work of all investigators involved in a study. An NCI official said investigators' desire for information on other studies involving their drugs has been recognized and NCI began distributing summaries of all studies on individual drugs to each investigator in late summer 1982.

NCI has recognized the need for improved reporting by investigators and is planning to experiment with direct data input to the contractors using computer terminals. NCI expects to achieve both more complete and more timely data input from investigators. Investigators will have an incentive to make their data inputs complete and up to date because they will be able to access the results of the other protocols besides their own in a particular drug study and perform data analyses using data from the entire study. An NCI official believes the cost of a direct input terminal system would be relatively small, but NCI has not made an estimate of the total costs involved.

SITE VISIT MONITORING OF NCI'S IND TESTING COULD BE IMPROVED

Site visits by drug sponsors to monitor their investigators' performance are an important means of determining whether patients are treated safely during IND clinical drug tests. As of March 1983 the site visit monitoring of some phases of NCI's clinical drug studies appears generally adequate, but for others it should be improved. The site visit monitoring procedures for NCI's phase I cytotoxic drug studies are generally satisfactory, and NCI has required frequent site visits by its monitoring contractor to these phase I investigators. However, some of NCI's phase II and III drug studies are not site visited, while others may not be visited often enough. NCI has recognized for some time the need to expand its site visit monitoring to more of its drug studies and has made plans to do so.

Onsite monitoring by sponsors is an important means for determining whether investigators are (1) following drug study protocols, (2) reporting accurate data to sponsors on study results, (3) properly accounting for their drug supplies, (4) reporting patients' ADRs, and (5) following proper informed consent procedures with patients. Patient safety during clinical drug testing is directly related to the way investigators perform these responsibilities.

The site visit monitoring procedures used on NCI's phase I cytotoxic drug studies generally appear adequate as does the scheduled frequency of site visits for these trials. NCI employs a private contractor to perform the monitoring of its phase I studies. Beginning in September 1982, the monitoring contractor started to make three visits a year to each investigator. One visit is made by a physician and includes verification of (1) required IRB approvals of the study and of patient informed consent forms, (2) accuracy of data submitted by the investigator to NCI, (3) investigator adherence to FDA-approved protocols, and (4) controls over drug supplies. Data accuracy is verified by comparing test results and eligibility information submitted to NCI with a sample of patient files (referred to as a data audit).

Protocol adherence is verified by comparing protocol requirements for testing and eligibility with these patient files. Pharmacy procedures and controls over drug storage and issuance are reviewed, including a sample comparison of what pharmacy logs show were issued (prescribed) to patients with what official patient records show. The other two visits made each year to each phase I investigator are done by a clinical research associate who performs data audits on a sample of patient records. Patient record sample sizes in all cases are to be no less than 10 percent of the patients in the investigator's study.

NCI did not, as of March 1983, require site visit monitoring for its phase I clinical tests other than for cytotoxic drugs or for those phase II and III studies which are not performed by one of its cooperative study groups. (See p. 35.) NCI plans to have site visit monitoring of these investigators beginning sometime in 1983. The phase I investigators will be visited by NCI's private contractor. The phase II and III investigators will be visited by peer physicians selected from the phase II and III investigators and accompanied by a clinical research associate from the NCI private contractor.

NCI's cooperative study groups which perform many of NCI's phase II and III clinical drug studies are currently (as of March 1983) visited on a peer review basis, according to an NCI official. Investigators and staff from each group are selected

to make visits to each other to monitor the same things covered by NCI's private contractor on phase I studies. NCI has issued site visit guidelines to each group and has received each group's specific site visit procedures. NCI receives reports on the results of site visits, according to this official. The only change NCI plans for these site visits to its cooperative study group investigators is that a clinical research associate or a physician from NCI's private contractor or an NCI official will observe the site visits by the peer review teams for about 30 percent of the visits. The observer will report back to NCI on the results.

NCI's planned expansion of its site visit monitoring is a positive step, but it may not go far enough. For example, NCI had no plans as of March 1983 to monitor the estimated 2 dozen investigators conducting its studies in foreign countries. An NCI official said the cost of trips to site visit NCI's foreign investigators is too great for NCI's budget.

Also, NCI's planned frequency for site visits to its phase II and III investigators may not be often enough to ensure that investigators are performing properly. Currently NCI plans that monitors will make site visits on an average of once every 3 years to each phase II and III investigator. This is less frequent than NCI's requirements for site visits to its phase I investigators, who are visited three times a year. Also, according to an NCI survey, it is less frequent than private companies are averaging for their site visits to investigators--once every 7 weeks.

NCI's planned monitoring of its phase II and III studies may be even less frequent than an average of once every 3 years. Some investigators have more than one NCI clinical drug study under way. In these cases, because of time and resource constraints, NCI plans to select only a sample of the investigator's drug studies for monitoring. Some clinical drug studies, therefore, may be visited less than once every 3 years. Furthermore, the work of some individual investigators may not be monitored during site visits even if the drug study they are participating in has been selected for review. This is possible because several investigators may participate in one drug study protocol, but the relatively small number of patient files to be reviewed (10 to 20) may not be great enough to ensure that at least some patients under each investigator are reviewed.

An NCI official said the cost of more frequent site visits by monitors would be too great for NCI's budget. This official believes that NCI's less frequent site visits are offset by the random process it will use to select the investigators to be visited. Under the random selection process investigators will

never know when they will be visited during any 3-year period or which of their clinical drug studies will be selected for review. It is also possible under this process that an investigator may be selected more than once during the 3-year period. Because the investigators will never know when or how often they will be selected for a site visit, they will constantly be subject to such a visit. This will prevent investigators from becoming complacent in their conduct of clinical drug studies according to the NCI official.

NCI CAN IMPROVE CONTROLS OVER DRUG ACCOUNTABILITY

Although NCI has good controls over its process for handling drug requests from its investigators, it currently (as of March 1983) does not have adequate controls to ensure that drug shipments are received and used by its investigators only for authorized purposes. NCI has recognized for some time that it needs better accounting controls over its investigators' drug supplies and has made plans to improve the situation.

NCI drug request and shipment authorization procedures help ensure that only authorized investigators with approved INDs and active drug protocols can order NCI experimental anticancer drugs. Investigators order drugs on special order forms. When received at NCI, the forms are logged in and verified regarding IND, protocol, and investigator status, including investigator shipping address, drug dosage form, reasonableness of drug quantity orders, and order frequency. After any discrepancies between the order form and the NCI file data regarding these items are resolved, the approved order is sent to the NCI drug laboratory contractor who ships the drug by one of several means--air express, postal service, or common carrier--depending on the size of the order and the urgency.

NCI's drug controls currently (March 1983) do not provide for verification that drug shipments are received and placed in inventory by investigators. Basically, NCI relies on the investigators who place the drug orders to inform them when a shipment is late or missing; but investigators cannot always be relied on to notify NCI about missing shipments. For example, at each institution visited we examined shipment and inventory records for the six NCI-sponsored drugs covered by our review. Of the 141 shipments reviewed, we found one instance where 100 vials of an NCI-sponsored drug were shipped by NCI to an investigator but were apparently never received or reported as missing to NCI. The shipment was an emergency order which the investigator needed to maintain his supply until a normal order already in process could be delivered. The investigator's staff neglected to notify NCI that the emergency order never arrived. The order has never been accounted for.

In another instance we found that the number of drug vials shipped by NCI on one order was not correctly recorded in the institution's pharmacy inventory records. The shipment contained 60 vials, but the pharmacy inventory record showed only 28 vials received. Part of the difference may have been accounted for when the institution took a physical inventory about 8 months later and found 16 additional vials. Sixteen vials, however, have never been accounted for.

The lack of a positive drug receipt verification system opens the possibility for unauthorized diversion of drug shipments. If someone at an investigator's location sends in an unauthorized drug order on the proper form and is there to receive and divert the shipment when it arrives, neither NCI nor the investigator would realize what had happened.

The only controls NCI currently has which might prevent this are judgments made at the time an order is received on the reasonableness of the order's size and frequency. However, an NCI official stated that because the size of patient groups receiving the drugs tends to change at irregular rates, this process is not very reliable.

In addition to its lack of controls to verify that investigators receive the drugs it ships to them, NCI does not at present (March 1983) know whether some of its investigators are using the drugs they receive only for authorized purposes. Although NCI does have site visits made to many of its investigators to examine drug security procedures, to observe physical inventories of drugs, and to verify a sample of drugs disbursed (prescribed) to patients, it does not currently (March 1983) visit all of its investigators (see p. 38).

In addition, some types of drug disbursements shown on investigators' drug records are not verified during site visits to investigators. Currently investigators' drug disbursements to satellite locations participating in the study are not verified, nor are drug quantities shown on the investigators' records as returned to NCI. Without verification it is possible for an investigator to divert drugs to unauthorized uses without detection.

NCI plans to improve controls

NCI plans to improve its controls over drug accountability and has started by devising a standardized drug accountability form to be used by all its investigators. The form, which was issued to NCI's investigators in February 1983, will be used to provide a continuous inventory record for drugs by individual protocol showing all receipt and disbursement activity. This

includes dosages issued to individual patients, drug quantities sent to satellite institutions, and drug quantities returned to NCI.

NCI plans to have monitors verify the drug inventory balance disbursements and receipts shown on the new standardized forms during site visits to the investigators. The drug inventory balance shown on the form will be verified by a physical inventory. A sample of drugs disbursed to patients (prescriptions) shown on the form will be verified to individual patient records. Drug quantities shipped by NCI to the investigator and drugs returned to NCI by the investigator will be compared to the form. NCI has not as yet determined how it will verify drug disbursements by investigators to satellite locations as recorded on the drug accountability form, but an NCI official said the problem is being studied. According to this official, NCI may ultimately require that all satellite locations on a study obtain their drug supplies directly from NCI but as of now NCI only recommends this to its investigators.

Although NCI did not have monitors making site visits to all its investigators as of March 1983, it plans to do so this year except for its foreign investigators (see p. 40). NCI's planned frequency for site visits by monitors to its phase II and III investigators may not be often enough to ensure that investigators are receiving and dispensing the drugs only for authorized purposes (see p. 40).

FDA NEEDS TO FINALIZE SPONSOR-MONITORING REGULATIONS

The primary monitoring responsibility for IND studies rests with the drug sponsor, but FDA's current regulations do not specifically describe what that responsibility entails. Without such regulations drug sponsors may not always provide the degree of monitoring FDA considers necessary to assure patient safety. Past FDA and GAO[4] studies have shown deficiencies in clinical investigator performance which could have been detected and possibly deterred by proper sponsor monitoring. The studies led FDA to propose sponsor monitoring regulations in 1977 (42 Fed. Reg. 49, 612(1977)), but as of August 1983 they had not been finalized. An FDA official stated that the originally proposed regulations have been modified by changing some of the requirements to guidelines.

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[4]"Federal Control of New Drug Testing Is Not Adequately Protecting Human Test Subjects and the Public" (HRD-76-96, July 15, 1976).

Our July 1976 report and a 1974 FDA study found examples where clinical investigators had not:

--Followed approved protocols regarding patient eligibility for studies and required patient testing.

--Maintained accurate records of patient laboratory and treatment results.

--Accounted for drugs received from sponsors and administered to patients.

--Followed proper patient informed consent procedures.

In response to these studies, FDA indicated it would implement regulations specifying sponsors' monitoring obligations in lieu of increasing its own monitoring of clinical studies. The proposed regulations, which were published for comment in September 1977, would require sponsors to (1) submit to FDA written procedures for monitoring investigations, (2) assure that the investigator clearly understands his obligations before participation, (3) visit the investigator periodically to assure that the protocol is being adhered to, (4) receive written approval of an IRB where applicable before initiating the investigational study, and (5) maintain accurate accounting procedures and records. FDA concluded that this approach would place monitoring responsibility with the sponsors, where it belonged, and enable FDA to verify the performance of all investigators while investing fewer resources.

The proposed regulations had not been finalized as of August 1983. FDA officials indicated that the FDA Commissioner has been replaced three times during this period, substantially affecting the momentum needed to finalize the regulations. During its review of a draft of this report, FDA officials advised us that the issues addressed by the proposed regulations are very complex with no clear-cut right or wrong answers. They said that FDA has been working continuously to resolve these problems. Thus, 7 years after FDA recognized the need for improved monitoring of clinical studies, the regulations which would specify sponsors' monitoring requirements have still not been issued.

FDA SHOULD STANDARDIZE PROGRESS REPORTING REQUIREMENTS FOR DRUG SPONSORS

FDA regulations require sponsors to submit progress reports to FDA on their investigational new drug studies (see p. 34). The regulations do not contain guidelines or minimum requirements for information. Consequently, sponsor progress reports

vary significantly regarding the information presented. We found examples of reports submitted by sponsors for the 10 drugs included in our review which presented comprehensive information on the progress and status of the clinical studies and others which presented little information.

The least informative progress report we found was one page long and presented information on only the protocol number, investigator's name, type of study ("clinical pharmacology"), anticipated number of patients, and study status ("in progress"). Most of this information could have been obtained from the original IND application. No information on progress or results was presented. Among the best progress reports we found was a 13-page NCI report which presented detailed information by protocol on the number of patients treated, drug dosage levels, protocol amendments, toxicities encountered, and ADRs. It presented a good overall picture of what had happened for the period covered. NCI took action in 1982 to further improve the quality of its drug progress reports by developing report writing guidelines for the use of its staff. This should help improve the completeness and quality of progress reports.

CONCLUSIONS

NCI's phase I computerized data base is not as complete or as current as it could be because not all drug investigators are submitting timely or complete data. The data base, therefore, cannot be relied upon to present an accurate picture of drug study progress. While recent data show some improvement, we believe additional improvement is needed.

As of March 1983, the site visit monitoring of some phases of NCI's clinical drug studies was generally adequate. However, NCI did not make site visits to monitor how some of its investigators were performing on their clinical drug studies and did not visit other investigators often enough. NCI recognizes the need for more site visits and plans to increase them.

NCI's drug accountability controls do not currently provide for (1) adequate verification that drugs shipped by NCI are received and inventoried by investigators, (2) adequate verification of investigators' drug disbursements to satellite locations and drug returns to NCI, and (3) site visits to some investigators.

NCI plans and has begun to implement improved drug accountability controls over its investigators but the plans have not resolved several problems. For example, there is no way to verify investigator drug disbursements to satellite locations and site visits to phase II and III investigators may not be frequent enough to determine whether the investigators are carrying

out their recordkeeping responsibilities and are making only authorized disbursements of their drug supplies.

Since 1976 FDA has recognized the need to improve the monitoring of clinical studies. To satisfy that need FDA developed proposed sponsor-monitoring regulations in 1977 but has not implemented them. We believe FDA should finalize its proposed sponsor-monitoring regulations to provide greater assurance that sponsors are monitoring clinical studies to the extent considered necessary to assure patient safety.

Because FDA regulations do not specify what information should be included in sponsors' drug progress reports to FDA, sponsors have not always submitted reports which provide FDA with meaningful information on the progress of the drug study. To ensure that progress reports are informative, FDA should establish requirements stating what the minimum acceptable drug study progress reporting requirements are. FDA should require detailed information on (1) the number of patients treated under each protocol, (2) toxicities encountered including ADRs, and (3) drug dosage levels attained, including maximum tolerated dose levels and dose limiting toxicities.

RECOMMENDATIONS TO THE SECRETARY OF HHS

We recommend that the Secretary require the Director of NCI to:

--Review the need for and usefulness of its drug study data base. If needed, NCI should require clinical investigators to submit data in a more timely and complete manner. If not needed, NCI should terminate the effort.

--Ensure that NCI's site visit monitoring includes all NCI investigators; devise a procedure to verify investigators' drug disbursements to their satellite locations or require that drug shipments be made directly to these locations by NCI, and if possible within allocated resources, increase the frequency of site visits to monitor investigators' performance.

We also recommend that the Secretary require the Commissioner of FDA to (1) issue final sponsor-monitoring regulations and (2) establish specific requirements for information to be included in progress reports submitted by sponsors of drug studies.

AGENCY COMMENTS AND OUR EVALUATION

In commenting on a draft of this report (see app. II), HHS said that the report does not accurately reflect the current NCI drug study monitoring system partly because NCI's peer review process is not mentioned. HHS said it considers the peer review process a vital component of NCI's monitoring policy.

The NCI peer review process referred to by HHS concerns the method of selecting investigators to receive NCI grants and contracts. It involves the review of written proposals of investigator credentials and past accomplishments. It is intended to ensure that the best investigators are selected to work on NCI drug studies.

While care in selecting investigators is important, proper monitoring of drug studies once they are underway is also important to patient safety and it is this type of monitoring which our report addresses. Peer review selection of investigators should not be considered a substitute for adequate monitoring of ongoing drug studies.

HHS, in response to our recommendation to review the need for and usefulness of NCI's drug study data base, said the data base is both useful and needed. HHS said NCI's data base contractor has recently achieved better data reporting from investigators and that about 80 percent of the data are now reported within 4 weeks. HHS agreed that an expanded capability to accept investigators' data reports by computer and allow investigators computerized access to the data base would be valuable and indicated that NCI was currently developing such a system.

HHS agreed with our recommendation that NCI's site visit monitoring include all NCI investigators. HHS said site visit monitoring has recently been expanded to include affiliate institutions as well as those in cooperative groups. Also, HHS said a standard reporting form has been instituted for site visits and that monitoring includes reviewing the (1) adequacy of informed consent procedures, (2) study approval by the local IRB, and (3) verification of the receipt and appropriate disbursement of investigational drugs.

HHS agreed with our recommendation that a system for verifying investigators' drug disbursements to their satellite locations be devised or that drug disbursements to satellite locations be made directly by NCI. HHS said a system is now in place for documenting the disbursement of drugs from principal investigators to affiliated investigators.

While HHS has made progress in developing procedures for verifying investigator drug receipt and handling, we believe additional improvement is needed to verify the shipment of drugs from principal investigators to satellite investigators. We believe that officials making site visits to monitor principal investigators' drug handling should verify with satellite investigators that drug shipments, as shown on the principal investigators' records, were in fact received by the satellites. Officials should either visit satellites or the satellites should provide the institution drug receipt information.

HHS did not agree that the frequency of site visit monitoring on phase II and III drug studies should be increased to the extent that resources will allow. HHS said that because each investigator is at risk in any given year for a site visit, the current average frequency for such visits (once every 3 years) is not inadequate. According to HHS, there is no way of knowing what an "adequate" level of monitoring is because it has never monitored these investigators before. HHS further said the planned average frequency of site visits may be unnecessary if the program currently being implemented fails to disclose significant problems.

The NCI random process for selecting investigators to be visited might be enough to offset the infrequent average of site visits (once every 3 years) if all investigators and studies were visited in that period. However, as we pointed out (see p. 40) some studies and investigators may not be visited even once every 3 years under the current plan.

We are concerned with HHS' comment that the current frequency of site visits may be unnecessary if the initial round of site visits fails to disclose significant problems. Entire drug studies could be started and completed before a monitor visits the site even under the current 3-year average of visits. Private drug companies make site visits to their investigators on an average of once every 6 weeks, and NCI requires site visits to each of its own phase I investigators three times a year. In our opinion, NCI should not reduce the site visit frequency to its phase II and III investigators below what is already a very low level.

HHS agreed with our recommendation that FDA (1) issue final sponsor-monitoring regulations and (2) establish specific requirements for information to be included in progress reports submitted by sponsors of drug studies. HHS said that sponsor-monitoring regulations are currently undergoing internal review in preparation for publication and that the proposed new IND regulations will specify the required information for sponsors' progress reports.

APPENDIX I

United States Senate
COMMITTEE ON LABOR AND
HUMAN RESOURCES
SUBCOMMITTEE ON INVESTIGATIONS
AND GENERAL OVERSIGHT
WASHINGTON, D.C. 20510

December 7, 1981

The Honorable Charles A. Bowsher
Comptroller General of the U.S.
General Accounting Office
441 G Street, N.W.
Washington, D.C. 20548

Dear Mr. Comptroller General:

I am writing to request your assistance in the Subcommittee's continuing inquiry into the drug development program of the National Cancer Institute (NCI) and the regulation thereof by the Food and Drug Administration.

The Subcommittee's investigation, which was initiated eight months ago, has revealed very serious and alarming deficiencies in the management and operations of the NCI's drug development program and of the regulatory program administered by FDA's Bureau of Drugs. Testimony and documentation presented at the Subcommittee hearings on November 3 and 6, 1981, established all too clearly that both programs have suffered from inaction, confusion, delay, frustration, and failure in communications within and between these programs. These conditions have contributed to life-threatening and fatal reactions suffered by cancer patients who were administered anticancer drugs in NCI-sponsored clinical trials, as was revealed in the Subcommittee's hearings.

In light of the severity of these problems and deficiencies and widespread use of anticancer drugs in hospitals and clinics across the Nation, I believe it is essential that a comprehensive study be undertaken to determine the adequacy of existing policy, practice and procedure within the Department of Health and Human Services and its sub-agencies to

APPENDIX I

protect human subjects who participate in Federally sponsored clinical trials. Further, I believe that such a study should include a comparison of the policy, practice and procedure exercised and executed by the FDA in regulating and monitoring Federally sponsored clinical trials of investigational new drugs as opposed to similar clinical trials sponsored by private and commercial interests.

Therefore, I am requesting that the GAO initiate a review and evaluation of these programs to determine the adequacy and effectiveness of existing mechanisms and programs to protect human subjects who participate in clinical trials of investigational new drugs.

Should you or your staff have any questions regarding this request, please have your staff contact Ms. Terri Parker of the Subcommittee staff at 224-8789.

Thank you for your cooperation and assistance in this matter.

Sincerely,

Paula Hawkins

Paula Hawkins
United States Senator

PH:jm/dk

DEPARTMENT OF HEALTH & HUMAN SERVICES Office of Inspector General

Washington, D.C. 20201

JUN 13 1983

Mr. Richard L. Fogel
Director, Human Resources
Division
United States General
Accounting Office
Washington, D.C. 20548

Dear Mr. Fogel:

The Secretary asked that I respond to your request for our comments on your draft of a proposed report "More Can Be Done to Protect Patients During Clinical Testing of Anticancer Drugs." The enclosed comments represent the tentative position of the Department and are subject to reevaluation when the final version of this report is received.

We appreciate the opportunity to comment on this draft report before its publication.

Sincerely yours,

Richard P. Kusserow
Inspector General

Enclosure

APPENDIX II

COMMENTS OF THE DEPARTMENT OF HEALTH AND HUMAN SERVICES ON THE COMPTROLLER GENERAL'S DRAFT REPORT, "MORE CAN BE DONE TO PROTECT PATIENTS DURING CLINICAL TESTING OF ANTICANCER DRUGS," REPORT NO. HRD-83-52, DATED MAY 2, 1983

General Comments

We have reviewed General Accounting Office's (GAO's) draft report and are pleased to note its generally favorable tone. We agree with GAO that certain administrative improvements are needed and in our comments to specific recommendations have outlined actions we have and will be taking to continue to assure that risks to patients are minimized. Before discussing these actions we would like to point out several concerns we have with the report.

First, and most importantly, the report could appear to incorrectly imply that cancer patients have been or are being exposed to "unnecessary risk." Although GAO does contend that the Food and Drug Administration (FDA) cannot be assured that patients have not been exposed to unnecessary risk (due largely to inadequate recordkeeping), procedural deficiencies which "could" or "might" imply risk do not establish risk. This distinction should be made.

For example, although the report expressed concern about FDA's timeliness in circulating Investigational New Drugs (INDs) to the scientific reviewers, the record indicates that in virtually all of the cases there still was ample time to perform the 30-day safety review prior to the initiation of the clinical study. Of the 3,336 INDs received for all drug categories from October 1980 through March 1983, only four were not reviewed within the 30-day limit.

In a second example, the report notes that only after receiving a report of a patient death did FDA learn that a particular drug investigation was being performed under protocols that had not been previously submitted to the agency. The report quite properly does not conclude that the failure of protocol submission in any way "caused" the death in question. In studying life threatening diseases such as cancer, patient deaths are more likely to be the norm than the exception, a result attributable as much to the patient's disease as to the investigation of the drug, and reports of deaths, without more information, cannot reflect adversely on the sponsor, the drug, or the FDA. It is our view that it would be improper to draw an inference from this report that patients undergoing investigational cancer therapy have been or are subject to unnecessary or unreasonable risk because of the problems noted.

Secondly, the draft report does not accurately reflect the current system as it is now being administered by the Department. A number of procedures for clinical trials research at National Cancer

Institute (NCI) have been changed over the past several years, most especially since 1981. Of the ten experimental drugs examined by GAO, five of them entered clinical testing prior to 1981. While we understand GAO's reasons for including the older drugs in their review, we believe that if GAO's review had been limited to post-1981 drugs, this change in situation might more readily be seen. We note too that the report does not discuss NCI's peer review process, a vital component of NCI's monitoring policy.

Finally several important initiatives have already been undertaken within the Department which specifically address the investigational new drug process and, in some instances, testing of anticancer drugs in particular. They may be described as follows.

a. Public Health Service (PHS) Task Force on NCI-FDA Investigational New Drugs:

- agreement was reached between FDA's Divisions of Oncology and Radiopharmaceutical Drug Products and Scientific Investigations on a process for maintaining communication and awareness of the progress of oncologic drug investigations. The resulting agreement is already being implemented. At the same time NCI has devised and is implementing a substantially expanded and improved monitoring effort.

- Office of New Drug Evaluation (ONDE) reviewing staff were given briefings on the new Institutional Review Board (IRB) and new informed consent regulations to bring them up to date about the new role of the IRBs and their own role in reviewing INDs.

- NCI was provided a compilation of defects observed by FDA's Division of Scientific Investigations in their review of several months of informed consent statements voluntarily submitted by NCI (this is not a requirement of sponsors.)

- the delegations of authority to the Director, Division of Oncology and Radiopharmaceuticals to sign out IND/NDA related correspondence were confirmed so as to assure prompt communications on important application-related matters.

- a study was conducted among the oncology division reviewing staff regarding their perceptions toward the comparative quality of NCI versus drug industry submissions. The resulting report indicated that a substantial improvement in NCI submissions had already occurred and continuing further improvement was noted.

b. Management Study: FDA New Drug Approval (NDA) Study:

As a result of this April 1982 report prepared by Health and Human Services (HHS) Assistant Secretary for Management and Budget, a

number of actions have been taken to improve FDA's management system, procedures, and policies in the IND/NDA program area. Although these improvements apply equally to all the reviewing divisions, a beneficial impact on the oncology division will also result. For example, such efforts include a total reassessment of the management information systems available to FDA's Office of New Drug Evaluation (NDE) within the National Center of Drugs and Biologics (NCDB). The product of this reassessment could provide a basis for improved tracking of the status of sponsor's efforts to address deficiencies pointed out by reviewers.

c. IND Rewrite:

FDA's proposed revisions to the investigational new drug regulations will address many of the procedural and recordkeeping issues addressed in GAO's recommendations, as specified below. We recognize that this document was not made available to GAO staff prior to the preparation of this draft, but we do think it important to recognize that the Department, on its own initiative, is preparing a comprehensive revision of these regulations. We expect to publish these proposals soon in the Federal Register.

GAO Recommendation

We recommend that the Secretary direct the Commissioner of FDA to:

1. --Require that IND reviewers document for the record, within 30 days of the date an IND is submitted to FDA for initial review, that they have satisfied themselves as to the safety of patients participating in tests of new anticancer drugs.

Department Comment

We agree that documentation of the 30 day review is appropriate and current policy requires such documentation from each of the three disciplines, not only for anticancer drugs, but for all drugs. We will examine the extent to which this problem exists with regard to oncologic drugs by surveying the files for signed 30 day reviews in the division that handles them. FDA will issue a memo emphasizing the need for attention to the prompt processing of reviews by reviewers and expedited handling by document personnel.

GAO Recommendation

2. --Require that IND reviewers discuss all IND deficiencies with sponsors before clinical testing begins, or as soon as possible after a deficiency is noted if testing has already begun, and then communicate all such deficiencies in writing to the sponsor in a timely manner.

Department Comment

We do not concur that all IND deficiencies be discussed. It is currently the responsibility of reviewers to identify where an IND has critical deficiencies that necessitate its being placed on hold until the deficiencies are corrected. It is not necessary to immediately discuss with the sponsor deficiencies that do not importantly affect the safety of the planned study or its likely usefulness. These deficiencies may be resolved later. It is FDA's current practice to transmit important deficiencies promptly.

GAO Recommendation

3. —Establish a formal followup system so that FDA can know whether IND sponsors respond to its recommendations to improve patient safety.

Department Comment

While it would appear to be useful to have a mechanism for ascertaining whether sponsors have responded to all deficiencies, the need for a system as a supplement to the continued monitoring by reviewers of sponsor responses to notifications of deficiencies has not been demonstrated. We will however consider whether this is a problem and whether there is a reasonable way to do this within the limits of available resources.

GAO Recommendation

4. —Revise its regulations to require sponsors to approve and submit for FDA review, before clinical testing begins, all clinical protocols.

Department Comment

The new IND regulations that will be proposed soon explicitly address this point by requiring that sponsors submit an overall research plan with their initial submission and to submit new protocols before beginning clinical testing using the new protocols.

GAO Recommendation

5. —Develop a system for identifying major IND amendments and more promptly distributing them to reviewers.

Department Comment

We concur. The proposed IND rewrite regulation will allow this; it separates amendments into protocol amendments and information amendments each to be appropriately identified by the sender. The protocol amendments will be expeditiously handled in recognition of their greater potential importance.

APPENDIX II

GAO Recommendation

6. —We also recommend that the Secretary require the Director of NCI to advise FDA in a timely manner of actions taken or to be taken on concerns raised by FDA.

Department Comment

It is not necessary to impose any requirements in this regard because NCI has responded promptly to FDA concerns and will continue to do so. Therefore, no further initiative is required. Under the terms of the January 19, 1979 Memorandum of Understanding signed by the Director, National Institutes of Health (NIH). and the Commissioner of Food and Drugs, clear channels of communication were established between specific staff of Division of Cancer Treatment, NCI, and counterpart personnel at FDA. These communications, operating at both senior policy and operational staff levels, have been exceedingly effective, including frequent meetings of relevant staff on problems of mutual concern.

GAO Recommendation

We recommend that the Secretary require the Commissioner of FDA to:

7. --Give sponsors more precise guidance as to what types of reactions they should report as ADRs and when they should report ADRs in cases in which the reaction's relationship to the drug is uncertain. This should include specific timeframes for reporting ADRs to FDA.

8. —Urge sponsors, if they have not already done so, to establish definite timeframes for clinical investigator reporting of ADRs which will allow the sponsors time to meet FDA's reporting requirements.

9. —Instruct sponsors to label or otherwise highlight ADR forms or mailing envelope to insure that ADRs will be recognized and dealt with immediately upon their arrival at FDA.

Department Comment

The new IND regulations that FDA will propose do clarify the requirements for submitting adverse drug reaction (ADR) reports as well as set forth specific timeframes for the submissions. The new regulations also will require that reports of serious adverse effects be prominently identified for expeditious handling by FDA. As to investigators promptly informing sponsors of adverse effects, current regulations require this and the investigators must agree to do so as part of their IND agreement (see forms FD 1572 and 1573.)

It should also be noted that in 1981, NCI established a system for reviewing all reports of adverse drug reactions on a monthly basis. NCI staff examine each reported reaction to determine its probable

relationship to the experimental drug. Reports of serious reactions are required to be immediately transmitted to FDA as well as to other investigators using the suspected agent. Since initiation of this system, the number of reports has averaged 15 per month as compared to 2-3 per month prior to initiation of the system.

GAO Recommendation

We recommend that the Secretary require the Director of NCI to:

10. --Review the need for and usefulness of its drug study data base. If needed, NCI should require clinical investigators to submit data in a more timely and complete manner. If not needed, NCI should terminate the effort.

Department Comment

The data base is both useful and needed. Through the recent increased efforts of NCI's Phase I data contractor, Mathtech, reporting of Phase I data has increased markedly, from 58% of pertinent data from ongoing trials entered into the system to the current level of approximately 80% of the required data being reported within 4 weeks. We believe that with increasing familiarity and better communication, data reporting will increase even more. We also agree with GAO that an expanded capability to accept investigators' data reports by computer and allow them computerized access to the data base would be of considerable value. NCI is currently developing such a system.

GAO Recommendation

11. —Ensure that NCI's site visit monitoring includes all NCI investigators; devise a procedure to verify investigators drug disbursements to their satellite locations or require that drug shipments be made directly to these locations by NCI and if possible within allocated resources, increase the frequency of site visits to monitor investigators performance.

Department Comment

We concur in part, as follows:

A. Ensure that NCI's site visit monitoring includes all NCI investigators.

We concur. The clinical trials monitoring system, as it now exists, includes all clinical trial group members and satellite insitutions. Monitoring through site visits was initiated in a segment of NCI's cooperative group program in 1978, and during the last three years has been expanded to include investigators from Phase I to Phase III. In 1983, the site visit program has been further expanded to the affiliate institutions. As a part of the site visit process, the adequacy of informed consent procedures, approval by a local IRB, and verification

of the receipt and appropriate disbursement of investigational drugs are determined. A standard reporting form has been instituted for these site visits. We have received the wholehearted cooperation and support of our investigators in establishing the site visit process. We agree that the site visit process should be expanded to include investigators outside the clinical co-operative groups, and as stated in the report, plans are underway to implement such a system in July 1983.

B. Revise a procedure to verify investigators' drug disbursements to their satellite locations or require that drug shipments be made directly to these locations by NCI and if possible within allocated resources.

We concur. A system for recording all receipts and disbursement of experimental drugs has been instituted among NCI-sponsored clinical investigators as of January 1983, and will be examined during the regular clinical site visits. The NCI has implemented a plan to record the receipt and appropriate use of investigational drugs. We feel that significant strides have been made in terms of verifying the appropriate use of drugs. In addition, a system is currently in place for documenting the disbursement of drugs from principal investigators to satellite investigators.

C. Increase the frequency of site visits to monitor investigators' performance.

We do not concur. We do not agree that the frequency of site visits currently ongoing in the clinical groups (once every three years) is not adequate. Each investigator is at risk of a site visit in any given year because the investigators to be visited are selected randomly, and a site visit in one year does not guarantee that a site visit will not be made the next year. Secondly, since the clinical monitoring has never been done before, there is no way of knowing what will constitute an "adequate" level of monitoring. It could well be that current frequency will be unnecessary if the current round of site visits fails to disclose significant problems in the clinical trials network. We feel that this issue can only be answered by assessing the results of this first round of site visits.

NCI also has significantly tightened controls over the unfunded associated investigators who contribute significant numbers of patients to NCI trials. All such investigators are now listed with the NCI; they will also be selectively site visited on an accelerated basis over the next 12-18 months, and the requirements for informed consent, IRB approval, drug logs, and other verification measures will be the same as for our funded investigators.

APPENDIX II

GAO Recommendation

12. —We also recommend that the Secretary require the Commissioner of FDA to (1) issue final sponsor-monitoring regulations and (2) establish specific requirements for information to be included in progress reports submitted by sponsors of drug studies.

Department Comment

We concur. The sponsor-monitor regulations are currently undergoing internal review in preparation for publication. As to establishing specific requirements for information to be included in progress reports, the new IND regulations will specify the required information.

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